The American Journal of Medicine

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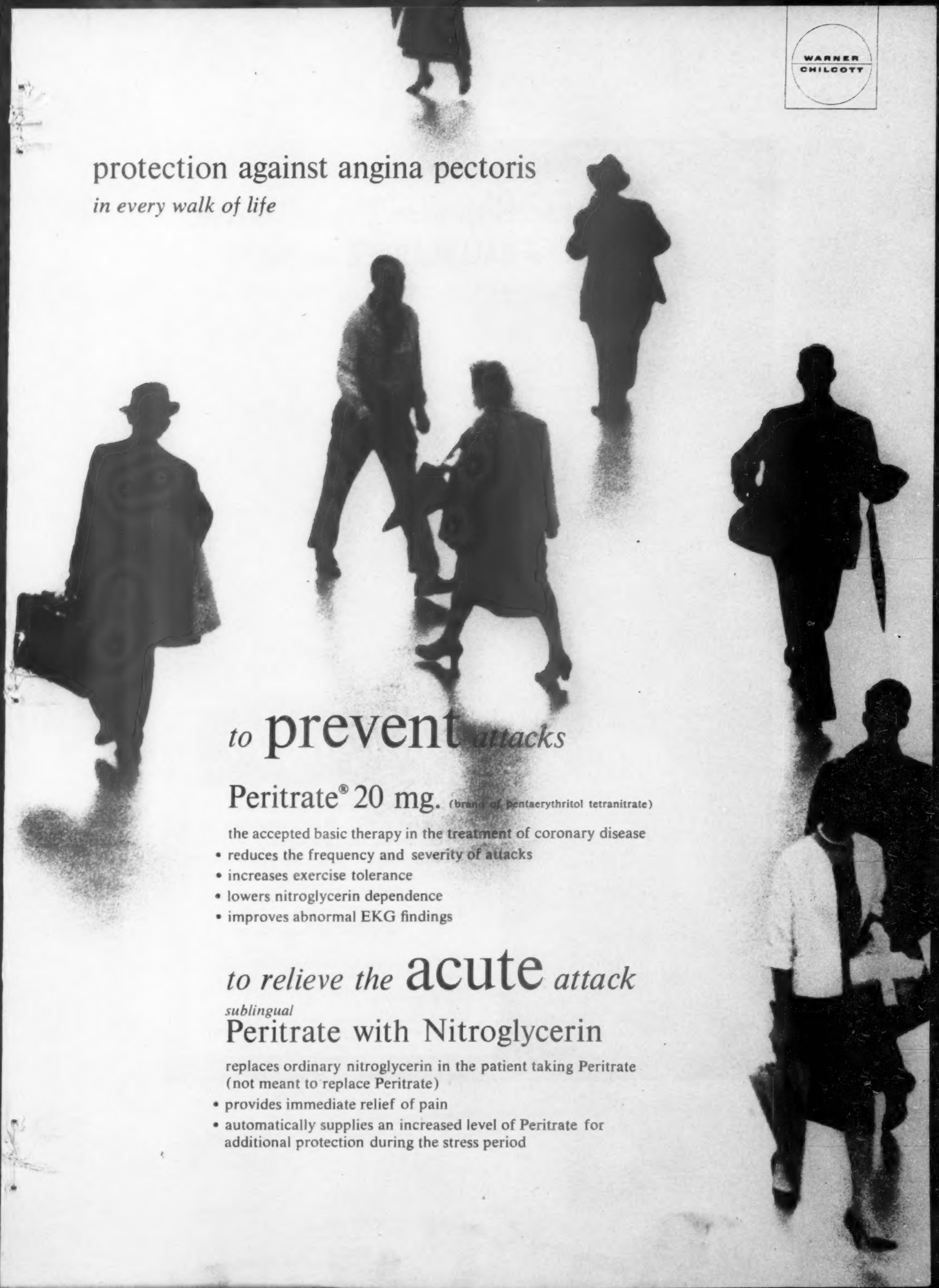

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protection against angina pectoris

in every walk of life

to prevent *attacks*

Peritrate® 20 mg. (brand of pentaerythritol tetranitrate)

the accepted basic therapy in the treatment of coronary disease

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- provides immediate relief of pain
- automatically supplies an increased level of Peritrate for additional protection during the stress period

The American Journal of Medicine

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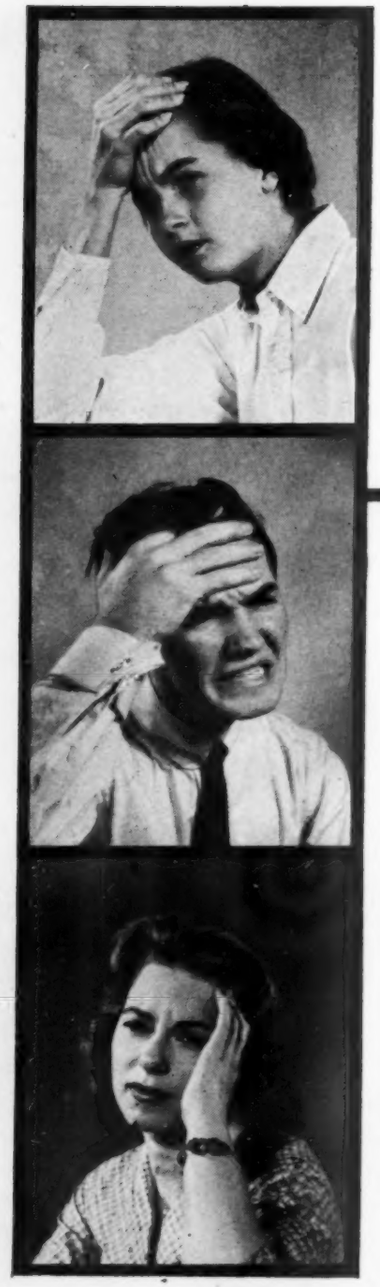

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Change of address must reach us one month preceding month of issue.

A STORY — by LUCY JONES

"Mommy had such an awful ache she had to go to bed"

"So I had to make dinner for Daddy. I even got the pills our doctor ordered"

"Then the pain went away real fast — almost before I finished the dishes"

"Now Mommy is fine... and she said I could help cook... but Daddy said just the tea"

FAST-ACTING ORAL BROAD-SPECTRUM THERAPY.

The modern blue and yellow ACHROMYCIN V Capsules, combining equal parts of pure crystalline ACHROMYCIN Tetracycline HCl and Citric Acid, provide unsurpassed oral broad-spectrum therapy.

Speed of absorption adds new emphasis to the benefits of true broad-spectrum action, minimum side effects and wide range effectiveness that have established ACHROMYCIN as an antibiotic of choice for decisive control of infection.

REMEMBER THE V WHEN SPECIFYING ACHROMYCIN V.

New blue and yellow capsules (sodium-free)—250 mg. with 250 mg. citric acid, and 100 mg., with 100 mg. citric acid.

ACHROMYCIN V dosage: Recommended basic oral dosage is 6-7 mg. per lb. body weight per day. In acute, severe infections often encountered in infants and children, the dose should be 12 mg. per lb. body weight per day. Dosage in the average adult should be 1 Gm. divided into four 250 mg. doses.

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to relieve edema of

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FINNERTY, F. A., Buchholz, J. H. and Tuckman, J.: J.A.M.A. **166**:141, Jan. 11, 1958.

DIURIL (Chlorothiazide) given alone to 85 patients, ". . . caused an excellent diuresis, with reduction of edema, weight, blood pressure, and albuminuria. . . . The average effective dose was found to be 1 Gm. per day by mouth. . . . The usually excellent response coupled with the absence of significant toxicity and lack of development of drug resistance makes chlorothiazide ideal for the prevention and treatment of toxemia."

DOSAGE: one or two 500 mg. tablets of DIURIL once or twice a day.

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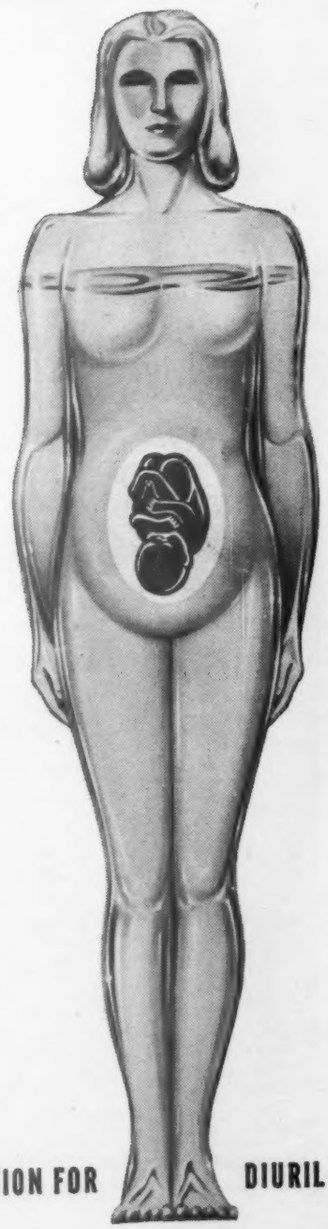
pregnancy

....caused an excellent diuresis, with reduction of edema, weight, blood pressure, and albuminuria...."



ANY INDICATION FOR DIURESIS IS AN INDICATION FOR DIURIL

SUMMARY OF REPORTS

No. of Patients	Results	Percent
6,553	Excellent	31.0%
10,843	Good	51.3%
2,703	Fair	12.8%
1,033	Unsatisfactory	4.9%

(Total Number of Side Effects: 638 [3.0%])

A NEW DIMENSION IN RESEARCH

This data deals with the results obtained by 1,988 physicians, treating 21,128 hypertensive patients with Unitensen. The "Proof In Practice" study validates, *in day-to-day private practice*, the findings of clinical trials conducted in hospitals and institutions. It proves that Unitensen affords safe, dependable office management for the majority of hypertensive patients. Unitensen lowers blood pressure . . . improves cerebral and renal blood flow... exerts no adverse effects on circulation . . . and, is virtually free of side effects.

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New Versatile Nuclear-Chicago Beta-Gamma Scintillation Probe

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Needle probes are provided in these sizes:
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For more than 12 years we have been designing and manufacturing for the medical profession high quality instrumentation for detecting and measuring radioactivity. We will be pleased to provide you with full information on the Model DS8 Scintillation Probe and on other Nuclear-Chicago instruments for clinical use.

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125 mg. per tsp. (5 cc.), 2 oz. bottle

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(orange-flavored) 5 mg. per drop,
calibrated dropper, 10 cc. bottle

COSA-TETRASTATIN*

glucosamine potentiated tetracycline with nystatin

antibacterial plus added protection against monilial superinfection

CAPSULES (black and pink) 250 mg. Cosa-Tetracyn, (with 250,000 u. nystatin)

ORAL SUSPENSION 125 mg. per tsp. (5 cc.) Cosa-Tetracyn, (with 125,000 u. nystatin), 2 oz. bottle

COSA-TETRACYDIN*

glucosamine potentiated tetracycline-analgesic-antihistamine compound

For relief of symptoms and malaise of the common cold and prevention of secondary complications

CAPSULES (black and orange) Ea. capsule contains: Cosa-Tetracyn 125 mg. • phenacetin 120 mg. • caffeine 30 mg. • salicylamide 150 mg. • buclizine HCl 15 mg.

REFERENCES: 1. Carlozzi, M.: Ant. Med. & Clin. Therapy 5:146 (Feb.) 1958. 2. Welch, H.; Wright, W. W., and Staffa, A. W.: Ant. Med. & Clin. Therapy 5:52 (Jan.) 1958. 3. Marlow, A. A., and Bartlett, G. R.: Glucosamine and Leukemia. Proc. Soc. Exp. Biol. & Med. 84:41, 1953. 4. Shalowitz, M.: Clin. Rev. 1:25 (April) 1958. 5. Nathan, L. A.: Arch. Pediat. 75:251 (June) 1958. 6. Cornbleet, T.; Chesrow, E., and Barsky, S.: Ant. Med & Clin. Therapy 5:328 (May) 1958. 7. Stone, M. L.; Sedlis, A., Bamford, J., and Bradley, W.: Ant. Med. & Clin. Therapy 5:322 (May) 1958. 8. Harris, H.: Clin. Rev. 1:15 (July) 1958.

– thank you, doctor"

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2. Most consistently elevated serum levels
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And now in practice

4. More rapid clinical response
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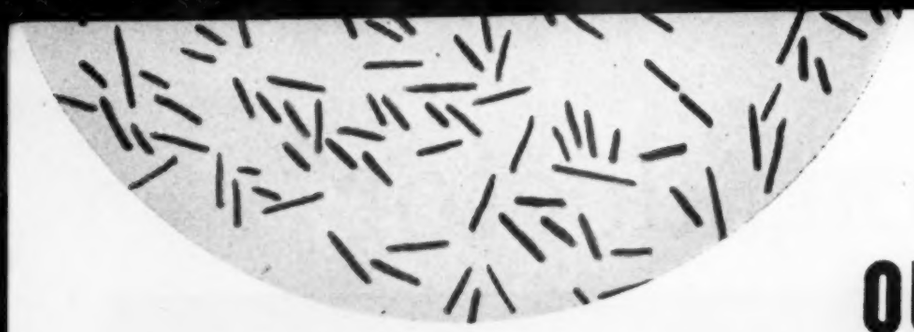

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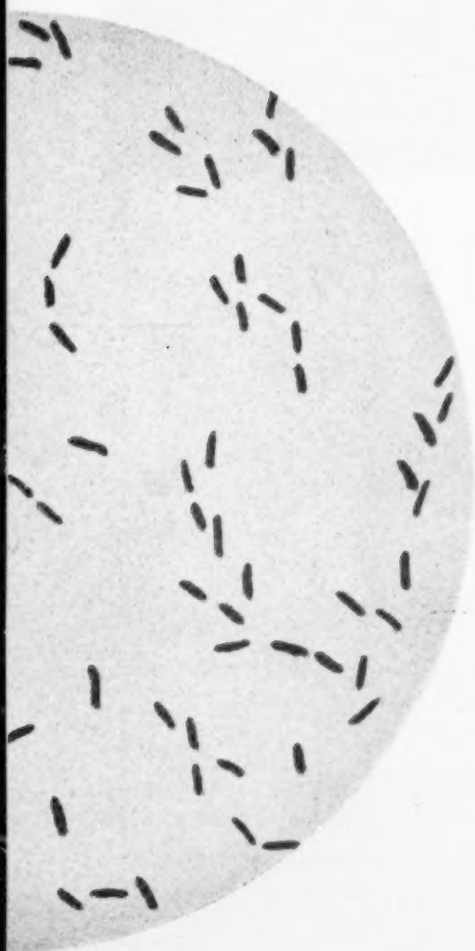
Numerous *in vitro* comparisons of antimicrobial activity show that CHLOROMYCETIN demonstrates outstanding effectiveness against both gram-positive and gram-negative organisms.[1-8] Clinically, it provides complete remission or improvement in patients with a wide range of infections, including pneumonias and other respiratory infections,[9,10] meningitis,[11] urinary tract infections,[12] salmonellosis and other gastrointestinal infections.[10,13]



CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES: (1) Waisbren, B. A.: *Wisconsin M. J.* 57:89, 1958. (2) Schneierson, S. S.: *J. Mount Sinai Hosp. New York* 25:52, 1958. (3) Markham, N. P., & Shott, H. C. W.: *New Zealand M. J.* 57:55, 1958. (4) Godfrey, M. E., & Smith, I. M.: *J.A.M.A.* 166:1197, 1958. (5) Caswell, H. T., *et al.*: *Surg., Gynec. & Obst.* 106:1, 1958. (6) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M. A. J.* 77:844, 1957. (7) Holloway, W. J., & Scott, E. G.: *Delaware M. J.* 29:159, 1957. (8) Ditmore, D. C., & Lind, H. E.: *Am. J. Gastroenterol.* 28:378, 1957. (9) Rosenthal, I. M.: *GP* 17:77 (March) 1958. (10) Ross, S.; Puig, J. R., & Zaremba, E. A., in Welch, H., & Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 803. (11) James, U.: *Brit. J. Clin. Pract.* 11:801, 1957. (12) Murphy, J. J., & Rattner, W. H.: *J.A.M.A.* 166:616, 1958. (13) Rabe, E. F.: *Pennsylvania M. J.*: 61:209, 1958.

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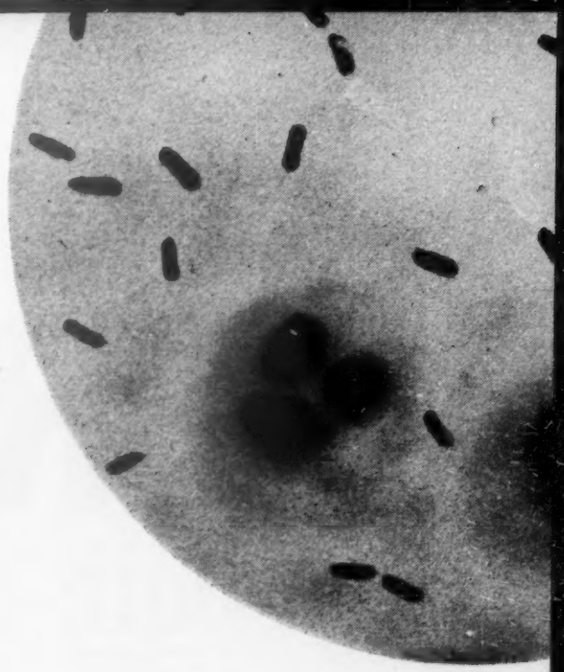
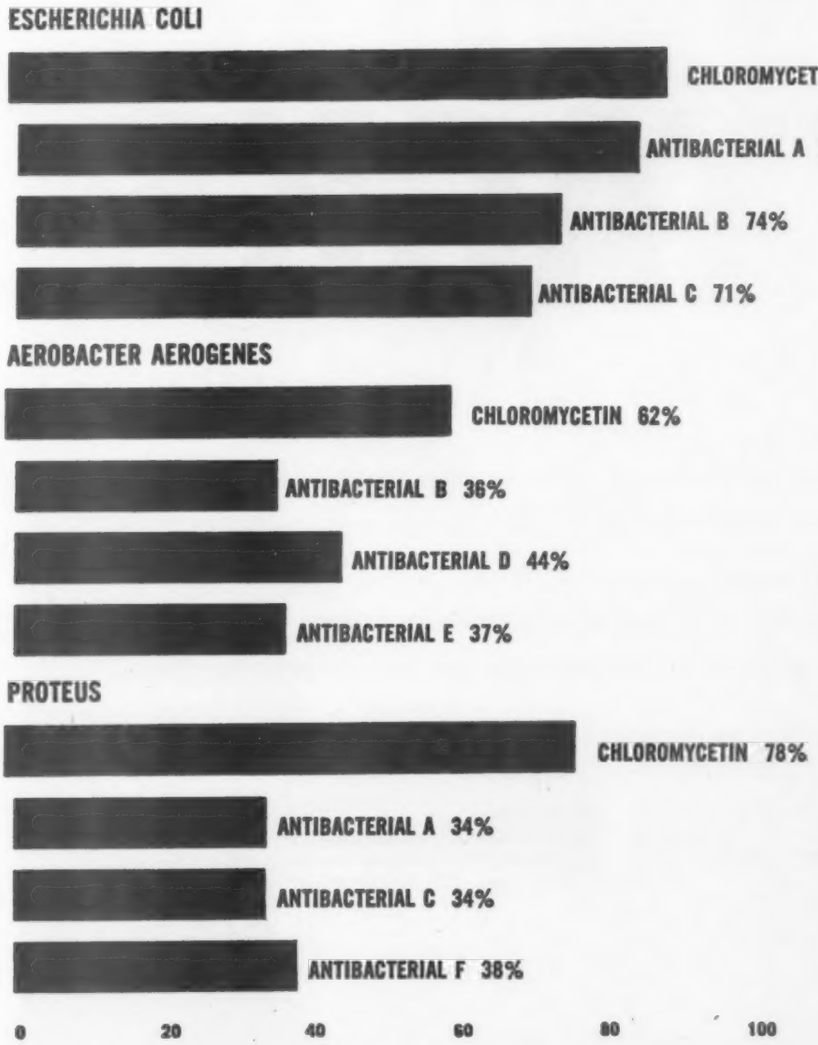


CETIN®

IN VITRO SENSITIVITY OF THREE GRAM-NEGATIVE PATHOGENS TO CHLOROMYCETIN AND TO OTHER WIDELY USED ANTIBACTERIALS*



*Adapted from Waisbren.[1]

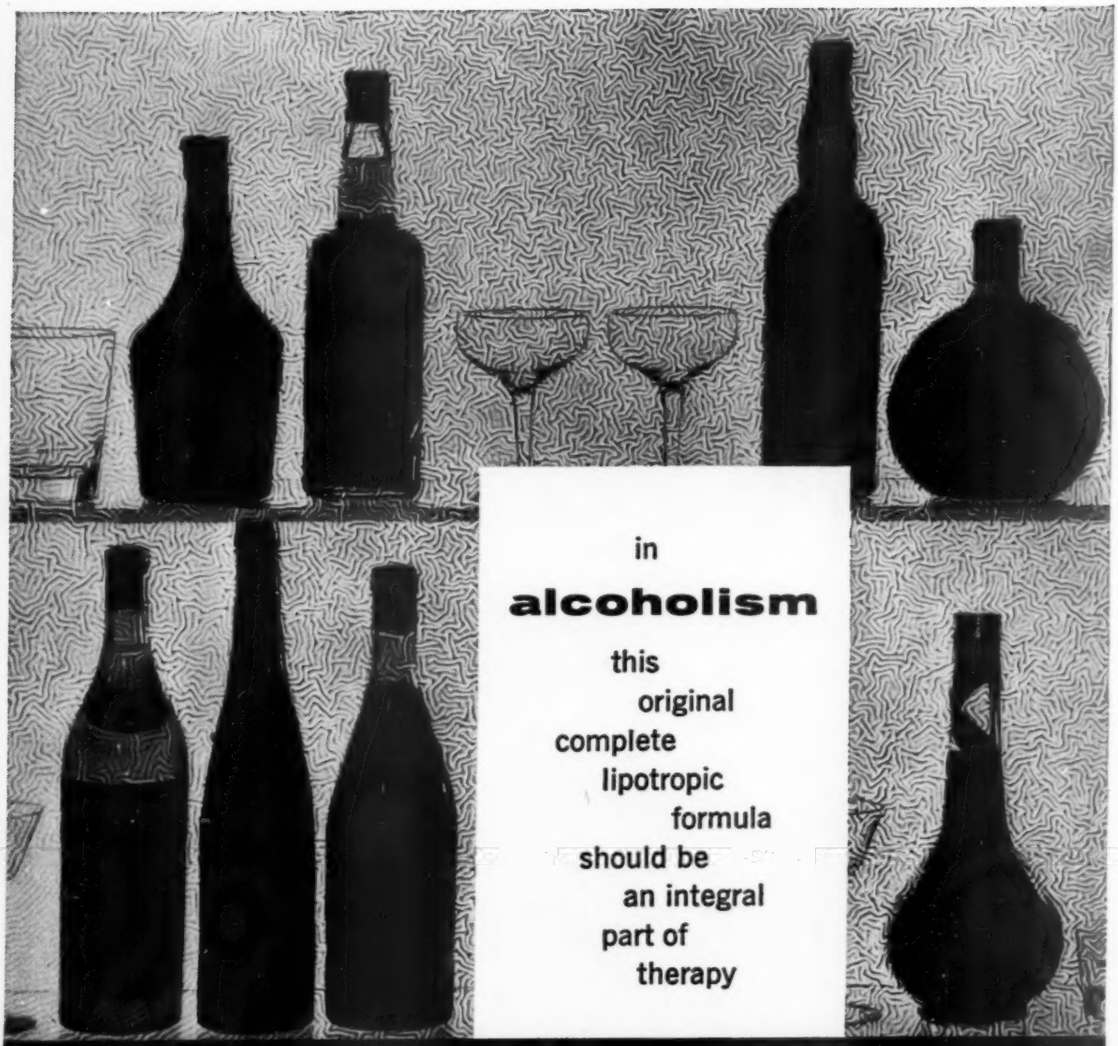
The antibacterial agents used in this study are those selected by the author as the ones most likely to be effective.

PREVENT
both cause and fear of
ANGINA ATTACKS

"In diagnosis and treatment [of cardiovascular diseases] ...the physician must deal with both the emotional and physical components of the problem simultaneously."[1]

The addition of Miltown to PETN, *as in Miltrate, "...appears to be more effective than* [PETN] *alone in the control of coronary insufficiency and angina pectoris."*[2]

1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* **1**:395, *March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:504, *Dec. 1957*



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alcoholism

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original
complete
lipotropic
formula
should be
an integral
part of
therapy

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to reverse and prevent further liver damage and hepatic cirrhosis (so common in alcoholism)

METHISCHOL helps to increase phospholipid turnover, reduce fatty deposits, lessen tendency to fibrosis and aids in regeneration of new liver cells.

as a protective aid against atherosclerosis and coronary impairment

METHISCHOL helps reduce elevated cholesterol levels and helps lower chylomicron-lipomicron ratios towards normal.

capsules bottles of 100, 250, 500 and 1000.
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THE ORINASE EPOCH

BREAKTHROUGH IN DIABETES

Just last year, a new chapter began in the treatment of diabetes: Orinase became available for general clinical practice. Today, more than 300,000 diabetics are enjoying the advantages of oral management.

What has our experience taught us? What has Orinase meant to practicing physicians, to patients, to investigators? What can we expect of the future?

That is

THE STORY OF ORINASE

ORINASE

BREAKTHROUGH IN DIABETES

When Orinase was first introduced, it was hailed primarily for the increased flexibility it lent to diabetic management, and for its patient benefits. The extensive experience of the past year has confirmed that Orinase is both safe and effective in the majority of adult, stable diabetics. But we now know that the significance of Orinase goes even further. Indeed, the new light Orinase has shed on our understanding of diabetes makes its advent a breakthrough comparable to the discovery, in 1889, that the diabetes syndrome rapidly develops following removal of the pancreas, and to the isolation of insulin in 1921.

Before Orinase, research in diabetes was moving ahead slowly. Pathogenesis of the disease remained an enigma, and the mechanism of insulin action continued to elude investigators. Nor was any explanation forthcoming for the different types of diabetic syndromes, the progressive nature of the disease, or for the wide range of insulin requirements.

Clinically, too, there was much to be desired: the lifelong regimen of daily injections, the rigid meal schedules, and, above all, the constant threat of hypoglycemia. To the patient, these meant a life centered around his disease; to the physician, the ever-present danger of complications.

And now, what are the circumstances one year after the introduction of Orinase? In briefest summary, this is where the evidence points:

1 **Diabetes mellitus does not appear to be a single pathological entity.** *There are several types of diabetic disorders. The most common is "Orinase-positive" diabetes, in which administration of Orinase induces release and utilization of the patient's* **endogenous** *insulin.*

2 **In "Orinase-positive" diabetics, Orinase achieves better control** *than injections of exogenous insulin.*

Facts and Figures

ORINASE

ONE YEAR AGO–1957

Orinase was officially released for prescription on June 3, 1957. Prior to its release, it had been thoroughly and painstakingly tested in more than 20,000 patients.

NUMBER OF PATIENTS ON ORINASE:	20,000
CRITERIA OF PATIENT SELECTION:	Adult, stable diabetes (onset around 40 years of age)
INCIDENCE OF SIDE EFFECTS: *(transitory skin rash, nausea, etc.)*	Only 3%
TOXICITY:	None
ESSENTIAL CONDITION FOR RESPONSE TO ORINASE:	Functional pancreas
PRIMARY MODE OF ACTION OF ORINASE:	Unknown
CONTRAINDICATIONS:	Juvenile diabetes…brittle diabetes…history of coma, acidosis, or ketosis…fever… severe trauma…gangrene…diabetes adequately controlled by diet alone.

ONE YEAR LATER–1958

Today, Orinase is a routine therapeutic agent in the management of hundreds of thousands of diabetics. Numerous clinical observations confirm its efficacy and have brought to light many new, additional benefits of Orinase therapy.

Over 300,000
Age: 40+ (at onset) Insulin: 40–(daily requirements) *These are typical criteria for the candidate most likely to respond to Orinase. However, diabetics with an earlier development of the disease also deserve a careful trial with Orinase, because Orinase has been found effective in many of the 20 to 40 age-of-onset diabetics.*
Approximately 3% (side effects continue to be mild and transitory–drug withdrawn for these effects in only 1.6%)
None
Functional beta cells of the pancreas
In the presence of a functional pancreas, Orinase effects the production and utilization of *native* insulin via *normal* channels.
Juvenile diabetes…brittle diabetes…history of coma, acidosis, or ketosis…fever…severe trauma…gangrene…diabetes adequately controlled by dietary restriction alone.

Objective advantages of Orinase

Intensive diabetic research, stimulated by the introduction of Orinase, has led many investigators to revise the very concept of diabetes as a single clinical entity, and to coin the term *"Orinase-positive"* diabetes. Oral therapy of *"Orinase-positive"* diabetics presents the following advantages:

Better control of diabetes

Orinase-responsive patients show more stable blood sugar levels and less glycosuria on Orinase than on insulin. Because Orinase acts via *endogenous* insulin, daily control of diabetes is smoother; "peaks and valleys" typical of exogenous insulin are leveled out.

Greater freedom from hypoglycemia

Patients on Orinase rarely experience hypoglycemic reactions. Even when hypoglycemia does occur, it is milder and more amenable to therapy than insulin (hypoglycemic) reactions.

Side effects—few and minor

Side effects attributable to Orinase occur in about 3% of cases, and only half of these necessitate withdrawal of Orinase. Most common are skin rashes or mild G. I. upsets.

No known toxicity

Careful observations of large series of patients maintained on Orinase for more than two years revealed no damage to the liver, blood, kidneys, or pancreas. Orinase is not goitrogenic.

Painless management of diabetes

Simple, easy, oral administration eliminates subcutaneous fat atrophy and frequent allergic reactions to insulin.

No increase in insulin requirements

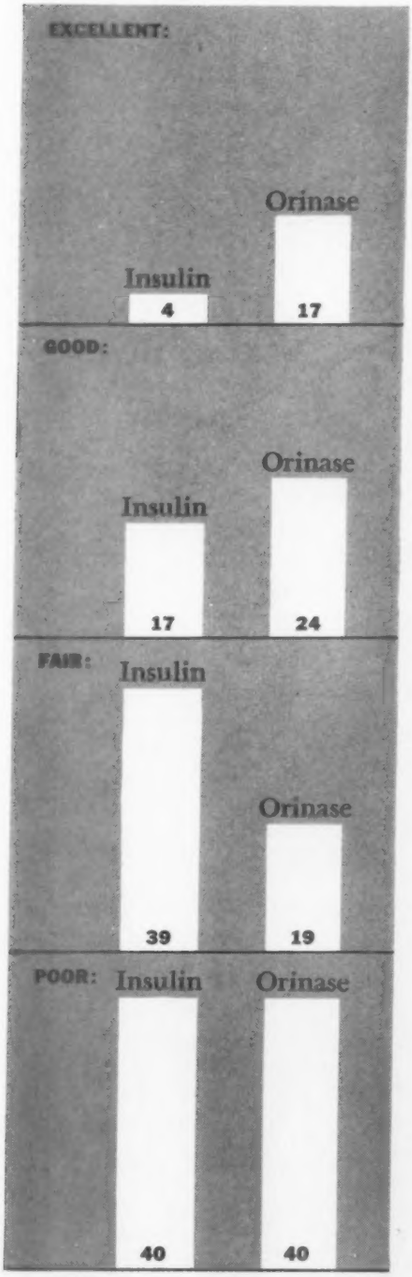
Even after prolonged Orinase therapy, patients scarcely ever show any increase in insulin requirements. In fact, such increase on Orinase is *less common than on insulin.*

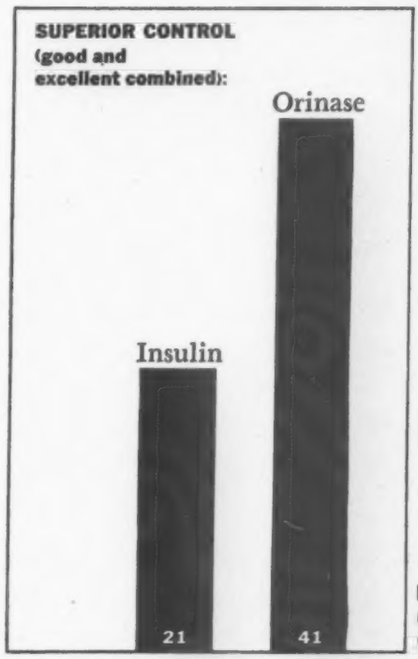
No impairment of diabetic status

Orinase therapy does not aggravate the underlying diabetic pathology. In some cases, there may be an actual improvement or even a remission.

QUALITY OF DIABETIC CONTROL IN 100 PATIENTS ON ORINASE COMPARED WITH CONTROL ON INSULIN[1]

Control rating:



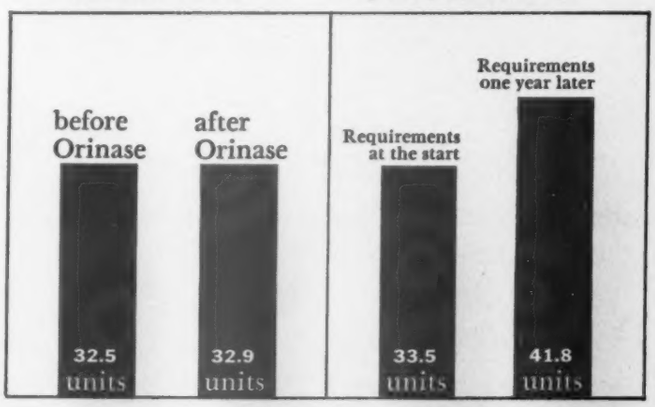


BETTER CONTROL OF DIABETES WITH ORINASE

NO INCREASE IN INSULIN REQUIREMENTS ON ORINASE[2]

Change in average insulin requirements of 30 diabetics resuming insulin after 1-15 months on Orinase

Change in average insulin requirements of 100 diabetics after one year of insulin alone



1. Based on the data of McKendry, J. B. R.; Kuwayti, K., and Sagle, L. A.: Canad. M. A. J. 77:429 (Sept. 1) 1957.
2. Based on the data of Pfeiffer, E. F.: J. Endocrinol. 15:xlviii (June) 1957.

Subjective advantages of Orinase

"The extreme satisfaction of patients whose conditions are now controlled with tolubutamide is immeasurable."

Breneman, J. C.: J.A.M.A. *164*:627 (June 8) 1957.

ORINASE HELPS TO CORRECT MAJOR DISLOCATIONS IN THE LIFE PATTERN OF DIABETICS

Orinase tends to restore emotional balance

Diagnosis of diabetes, usually coming late in life and carrying with it a long sentence of daily fear and anxiety, profoundly upsets the emotional balance of the average patient. Adjustment to radical changes in daily living is difficult. Daily injections, special meal schedules, and new limitations on activities make the patient feel "set apart." Oral therapy simplifies life, brings it closer to normal, helps restore a cheerful, hopeful outlook.

Sense of personal freedom regained on Orinase

No longer tied to a refrigerator, sterilizing apparatus, nearest restaurant, and rigid schedules, a diabetic on Orinase can enjoy travel and a variety of personal activities, free from the tyranny of the clock and the threat of hypoglycemia.

Orinase makes diabetes easier on the patient's family

With no dependence on members of the family for diabetic care, the patient can resume a more normal place in the family circle.

Orinase permits occupational continuity

Because of the hazards of hypoglycemic shock, some diabetics are forced to give up their customary occupations, or must limit and curtail their working hours—as may be the case with traveling salesmen, business executives, and others with unpredictable work schedules. On Orinase, patients usually can continue their normal occupations.

Normal social life made possible by Orinase

"Orinase-positive" diabetics can visit their friends, without the embarrassing necessity of meals at special hours...can participate in community life and social events in a more normal fashion.

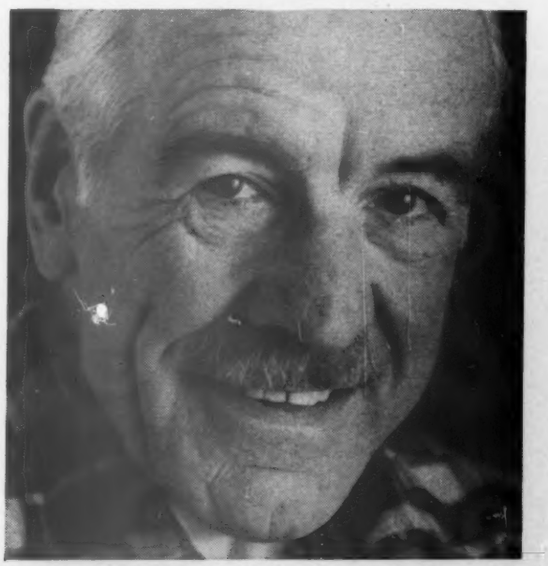
Stability and sense of well-being on Orinase

Patients report an increased sense of stability and well-being...they are less irritable...their mood and outlook are improved.

RETIRED BUSINESSMAN
Easier on the Patient's Family

GRANDMOTHER
Restored Emotional Balance

SCHOOLTEACHER
Sense of Personal Freedom



NEWSPAPERMAN
Occupational Continuity

A New Life in THE ORINASE EPOCH

MRS. B. G.—FEMALE—AGE 62

Mrs. B. G., a 62-year-old widow living alone, first manifested the overt symptoms of diabetes five years ago. Diagnosis was immediate and positive, with a blood sugar elevation of 250 mg. per 100 cc. and a urine of 4 plus, accompanying the typical signs of polyurea, polydipsia, and chronic fatigue. Placed on 40 units of lente insulin daily and a restricted diet, she responded well, maintaining an average postprandial blood sugar level of 145 and an average fasting blood sugar of 126.

Although her tests, chart, and periodic physical examinations indicated that her diabetes had been satisfactorily controlled, her physician from the outset was confronted with the problem that Mrs. G. was unable to adjust to the injection procedure. Exhibiting a classic example of "layman's fear of the needle," she refused to make an effort at self-administration, insisting that her married son do it for her. This need for help created a special hardship. It compelled her son, who lived 33 miles away, to rise each morning before six and drive to his mother's home to give her the injection, then make another long trip to his job. Because of the rigidity of her insulin requirements, Sundays and holidays offered Mrs. G.'s son no escape from this schedule. Moreover, he was unable to plan any trips or vacations for his family without including his mother.

The emotional stress induced by this situation was apparent in Mrs. G.'s behavior during visits to her doctor. Her remarks became preoccupied with her son and his family, revealing conflicting attitudes — petulance and resentment against the son for sometimes "coming late when he *knows* that I can't wait for my insulin," and for rushing through the injection procedure when "he *knows* how *sensitive* I am about it" — coupled with guilt feelings arising from awareness that she was disrupting her son's life. Periodically, her son

called Mrs. G.'s physician to ask whether any possible change in management might permit at least a temporary escape from the injection schedule.

The transfer to Orinase

The institution of Orinase management in this case brought about a significant change in the life situation, not only of the patient, but also of her son and his family. Mrs. G., although she realized that oral management would eliminate visits from her son for perhaps weeks at a time, welcomed the trial with Orinase. The transfer from insulin was smooth. Control has been well established on a dosage of 0.5 Gm. Orinase t.i.d., with a moderately restricted diet. On this regimen she has maintained an average postprandial blood sugar level of 140 and an average fasting blood sugar of 123.

In adjusting to oral medication, Mrs. G. has developed a sense of independence and security. The new regimen has done much to restore a healthy relationship with her son and his family.

This is one of a series of cases based on actual clinical data from the files of diabetes specialists and practicing internists, illustrating some of the changing aspects of diabetes control offered by oral management.

THE ORINASE EPOCH

BREAKTHROUGH FOR THE PATIENT

A more normal, more secure life for the majority of diabetics.

BREAKTHROUGH FOR THE PHYSICIAN

Smoother control, free from the danger of hypoglycemic shock.

BREAKTHROUGH FOR METABOLIC INVESTIGATORS

New stimulus and new evidence in searching for the final answers to diabetes.

ORINASE PRESCRIPTION INFORMATION

Dosage: Patients responsive to Orinase may begin therapy as follows:

First day . . . . . 3 Gm.
Second day . . . . . 2 Gm.
Third day . . . . . 1 Gm.

Usual maintenance dose . . . . . 1 Gm.
(must be adjusted to patient's response)

To change from insulin to Orinase:
If previous insulin dosage was

less than 40 u./day — reduce insulin 30% to 50% immediately; gradually reduce insulin dose if response to Orinase is observed.

more than 40 u./day — reduce insulin 20% immediately; carefully reduce insulin beyond this point if response to Orinase is observed. In these patients, hospitalization should be considered during the transition period.

Prior to using Orinase in selected patients, the physician should perform a complete physical examination and indicated laboratory studies. During the initial test period, the patient should report to the physician daily, and for the first month at least once weekly for physical examination and blood sugar determination. After the first month, the patient should be examined at monthly intervals or more frequently as indicated.

The patient should be instructed to report immediately to his physician if he does not feel as well as usual.

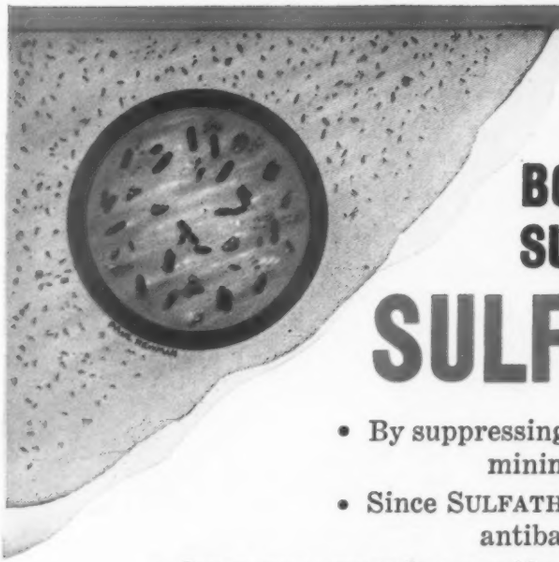
It is especially important that the patient, because of the simplicity and ease of administration of Orinase, does not develop a careless attitude ("cheating" on his diet, for example) which may result in serious consequences and failures of treatment.

Supplied: In 0.5 Gm. scored tablets, bottles of 50.

Complete literature available on request.

Upjohn The Upjohn Company, Kalamazoo, Michigan

ORINASE



FOR SAFER BOWEL SURGERY

SULFATHALIDINE®

PHTHALYLSULFATHIAZOLE

- By suppressing intestinal pathogens, SULFATHALIDINE minimizes a major danger in bowel surgery.
- Since SULFATHALIDINE is virtually nonabsorbable, its antibacterial effect is concentrated in the gut.
- SULFATHALIDINE has specific value as an adjunct in ulcerative colitis.

Available as 0.5 Gm. tablets in bottles of 100 and 1000—also as CREMOTHALIDINE®, a palatable suspension of SULFATHALIDINE. Each 30 cc. (1 fluidounce) contains 6.0 Gm. SULFATHALIDINE.

Sulfathalidine is a trade-mark of Merck & Co., Inc.

MSD **MERCK SHARP & DOHME**
DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

make poor eaters want to

"COME AND GET IT"

REDISOL®

CYANOCOBALAMIN (CRYSTALLINE VITAMIN B_{12})

REDISOL—vitamin B_{12}—used as a dietary supplement often stimulates appetite with consequent weight gain—youngsters look forward to their meals again.

Cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) and soluble REDISOL Tablets (25, 50, 100, 250 mcg.) mix readily with liquids.

Redisol is a trade-mark of Merck & Co., Inc.

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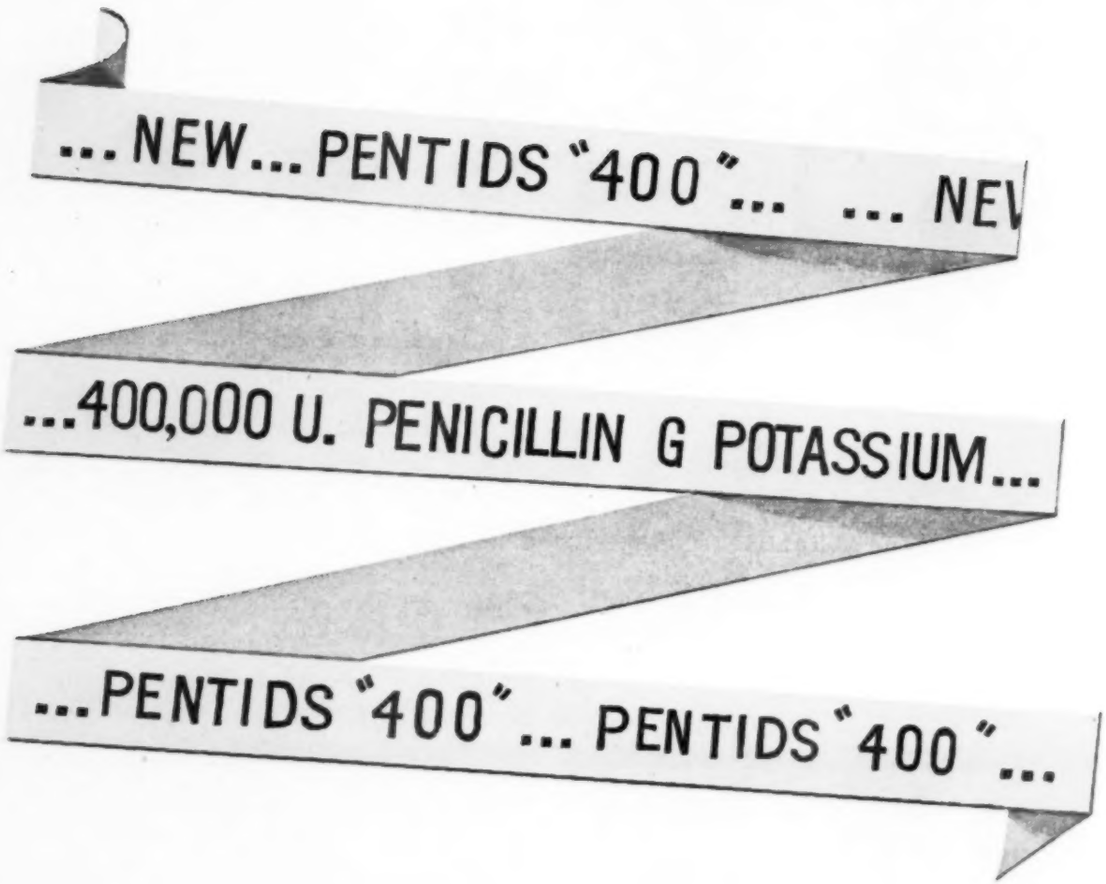


New convenient oral tablets . . . PENTIDS "400". . . Economical . . . where double strength Pentids is required for treatment of severe infections due to **Staphylococcus . . . Hemolytic Streptococcus . . . Pneumococcus.** Also indicated for prevention of streptococcal infections when there is a history of rheumatic fever. PENTIDS "400". . . Squibb Penicillin G Potassium 400,000 Unit Tablets (Buffered) . . . Dosage: 1 tablet t.i.d. without regard to meals . . . Supply: Scored tablets—bottles of 12 and 100.

For common bacterial infections, prescribe PENTIDS . . . 200,000 unit buffered Penicillin G Potassium Tablets . . . Dosage: 1 or 2 tablets t.i.d. without regard to meals . . . Supply: Scored tablets—bottles of 12 and 100.

PENTIDS® IS A SQUIBB TRADEMARK

Also available as . . .

Pentids for Syrup . . . Orange-flavored, provides 200,000 units Penicillin G Potassium per teaspoonful (5 cc.), 12 dose bottles . . . **Pentids Capsules** . . . each containing 200,000 units Penicillin G Potassium, bottles of 24 and 100 . . . **Pentids Soluble Tablets** . . . each containing 200,000 units Penicillin G Potassium, vials of 12 and bottles of 100 . . . **Pentids—Sulfas Tablets** . . . each containing 200,000 units Penicillin G Potassium with triple sulfas, bottles of 30 and 100.

SQUIBB

Squibb Quality—the Priceless Ingredient

this pediatrician needs Romilar CF

ROCHE

Romilar® Hydrobromide—brand of dextromethorphan hydrobromide

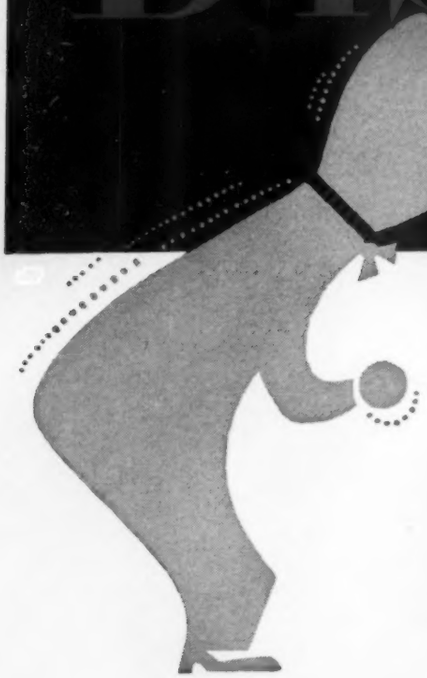
in Parkinsonism

The "HIGHLY SELECTIVE ACTION" of

Disipal®*

Brand of Orphenadrine HCl

"CANNOT BE DUPLICATED BY ANY OTHER CURRENT REMEDY"



"In a series of 176 patients...a valuable adjunct to therapy...highly selective action...that cannot be duplicated by any other current remedy ...effective as a euphoriant...and as an energizing agent against weakness, fatigue, adynamia, and akinesia...potent action against sialorrhea, diaphoresis, oculogyria, and blepharospasm... also lessens rigidity and tremor...minimal side reactions...safe...even in cases complicated by glaucoma."

Doshay, L.J., and Constable, K.: Treatment of Paralysis Agitans with Orphenadrine (Disipal) Hydrochloride: Results in One Hundred Seventy-Six Cases, J.A.M.A. *163*:1352 (Apr. 13) 1957.

in Skeletal Muscle Spasm

due to sprains, strains, herniated intervertebral disc, low back pain, whiplash injuries and many other painful skeletal muscle disorders, Disipal brings effective and prompt relief from spasm and pain. "The number of office visits...is reduced significantly. The dosage schedule is simple, and side actions are minimal."

Finch, J.W.: Clinical Trial of Orphenadrine (Disipal) in Skeletal Muscle Disorders. Scientific Exhibit at Mississippi Valley Medical Society Meeting, St. Louis, Missouri, Sept. 3-5, 1957.

Advantages

- Speedy relief of muscle spasm
- Orally effective
- Minimal side actions
- Mildly euphoriant
- Nonsoporific
- Tolerance no problem
- No known organic contraindications
- Economical

Dosage:
Usually 1 tablet (50 mg.) t.i.d.

*Trademark of Brocades-Stheeman & Pharmacia. U.S. Patent No. 2,567,351. Other patents pending.

Riker

NORTHRIDGE, CALIFORNIA

this pediatrician uses Romilar CF

When it comes to colds and coughs, pediatricians are no different from their patients . . . they all want to get rid of their symptoms and stay up and about, if possible.

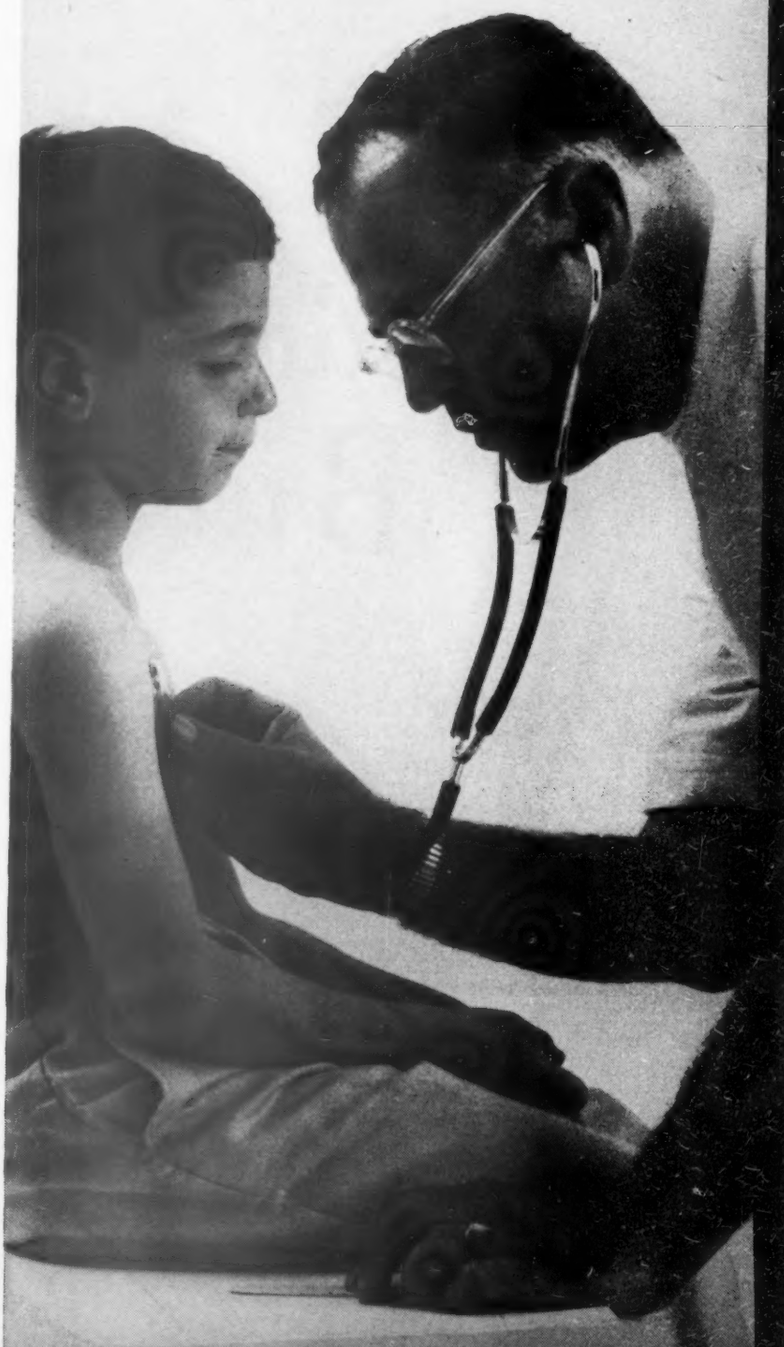
Romilar Cold Formula controls the entire symptomatology of colds, including coughs. A synergistic combination,* Romilar CF

checks coryza
suppresses coughing
relieves congestion
controls fever and malaise

Each teaspoonful (5 cc) of pleasantly flavored syrup, or each capsule, contains: 15 mg Romilar HBr (non-narcotic antitussive); 1.25 mg Chlorpheniramine maleate (antihistamine); 5 mg Phenylephrine HCl (decongestant); 120 mg N-acetyl-p-aminophenol (analgesic-antipyretic).

*L. O. Randall and J. Selitto, *J. Am. Pharm. Assn. (Sc. Ed.)*, 47:313, 1958.

Romilar® Hydrobromide—brand of dextromethorphan hydrobromide



ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc • Nutley 10 • N. J.

"Just a Sandwich"

But Such Excellent Nutrition

So often, people say, "I'll have just a sandwich." A sandwich made with Enriched Bread has nutritional advantages over many a knife-and-fork meal.

In addition to providing an excellent vehicle for other nutritionally valuable foods, the nutrient values of Enriched Bread add a definite plus for good nutrition.

Enriched Bread

supplies growth-promoting protein, readily available energy, important B vitamins (thiamine, riboflavin, niacin, pantothenic acid, choline, folic acid, and other B-complex factors), iron, and calcium.

•

Enriched Bread is more than a compatible vehicle for other foods; it is an effective provider of essential basic nutrients.

AMERICAN BAKERS ASSOCIATION
20 North Wacker Drive • Chicago 6, Illinois

for depression

▲Deprol▲†

Clinically confirmed in over 1,200 documented case histories[1,2]

CONFIRMED EFFICACY

Deprol ► acts promptly to control depression *without* stimulation

► restores natural sleep

► reduces depressive rumination and crying

DOCUMENTED SAFETY

Deprol is unlike amine-oxidase inhibitors

► does not adversely affect blood pressure or sexual function

► causes no excessive elation

► produces no liver toxicity

► does not interfere with other drug therapies

Deprol is unlike central nervous stimulants

► does not cause insomnia

► produces no amphetamine-like jitteriness

► does not depress appetite

► has no depression-producing aftereffects

► can be used freely in hypertension and in unstable personalities

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: Each tablet contains 400 mg. meprobamate and 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl).

Supplied: Bottles of 50 scored tablets.

1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Current personal communications; in the files of Wallace Laboratories.

†TRADE-MARK (D-740)

Literature and samples on request WALLACE LABORATORIES, *New Brunswick, N. J.*

X 125,000. Electron micrograph (courtesy of RCA).

The clue is in the crystals—
more than 5 times as adsorptive as kaolin

... crystals of Claysorb*, showing the tremendous surface area for adsorption. Because of Claysorb and its great adsorptive property, POLYMAGMA Plain rapidly removes intestinal bacterial toxins and irritants. Refreshing to the taste, POLYMAGMA Plain also soothes and protects the irritated mucosa; acts quickly on a low-dose regimen to restore normal intestinal function. (For infectious diarrhea, POLYMAGMA—same formula plus dihydrostreptomycin sulfate and polymyxin B sulfate.)

Supplied: Bottles of 12 fl. oz.

This advertisement conforms to the Code for Advertising of the Proprietary Council for Information on Child Health

NEW, MORE EFFECTIVE ANTIDIARRHEAL

Wyeth

Philadelphia, Pa.

Polymagma® Plain

Claysorb* (Activated Attapulgite, Wyeth) and Pectin in Alumina Gel

*Trademark

The ultimate today in therapy for menopausal disorders, menstrual disorders, inoperable breast cancer, male climacteric.

Ultandren™ (fluoxymesterone CIBA) *A new oral androgen tablet with 5 times the potency of methyltestosterone tablets.*

Ultandren presents a new range of possibilities for simple, convenient treatment in conditions stemming from certain types of hormonal imbalance. ■ *Small oral doses* provide full androgenic effects, previously obtainable only with parenteral testosterone preparations. ■ Easy tablet administration eliminates the painful injections, local reactions and skipped doses attending the use of intramuscular testosterone, as well as the foreboding aspects of treatment-room therapy. ■ Begin now to prescribe Ultandren, truly the ultimate today in therapy for menopausal disorders, menstrual dysfunction and premenstrual tension, male climacteric, and palliation of inoperable breast cancer.

SUPPLIED: ULTANDREN TABLETS, 2 mg. (light green, scored) and 5 mg. (violet, scored); bottles of 40.

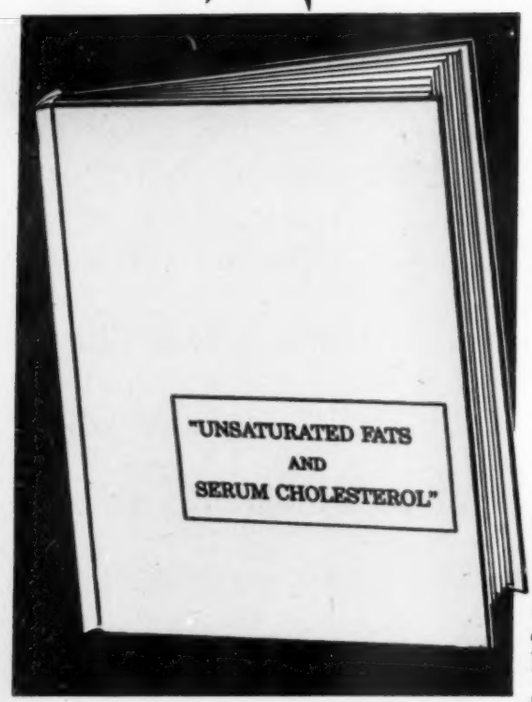
CIBA
SUMMIT, N. J.

2/2566MK

NEW BOOK . . . just off the press . . . send now for your FREE copy

"Unsaturated Fats and Serum Cholesterol"

A review of the latest concepts and results of current research



This new book contains the most up-to-date bibliography of current research on: 1. The origin and behavior of cholesterol in the human body; 2. The effect of different dietary fats on serum cholesterol levels; 3. The nature of the active components in vegetable oils; and 4. Suggestions for practical diets.

Now ready for distribution to Physicians by the makers of MAZOLA Corn Oil, this book supplements the 1957 monograph, "Vegetable Oils in Nutrition" and provides a broader coverage of this important subject.

As a regular part of daily meals

MAZOLA® CORN OIL

can be used for control of Serum Cholesterol levels

MAZOLA CORN OIL . . . the only leading oil made from golden corn, is rich in the important unsaturated fatty acids—When an adequate amount of Mazola is part of the daily meals, elevated serum cholesterol levels tend to be lowered . . . normal levels tend to stay level . . .

MAZOLA CORN OIL is a natural food, *and* cholesterol free, can easily be included as part of the every day meals . . . simply and without seriously disturbing the patient's usual eating habits . . . in salads, baking and other cooking processes.

Please use this coupon for ordering:

Medical Department
Corn Products Refining Company
17 Battery Place
New York 4, New York

Please send me a free copy of your latest reference book, "Unsaturated Fats and Serum Cholesterol."

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ADDRESS_____

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Technical Pamphlet, "Facts about MAZOLA Corn Oil," also available. Provides technical information on chemical and physical properties. Check here if you wish a copy of this pamphlet ☐

CORN PRODUCTS REFINING COMPANY

Each **TABLESPOONFUL** *of*
MAZOLA
Provides approximately:

LINOLEIC ACID	**7.4 Gm.**
Sitosterols	130.0 mg.
Natural tocopherols	15.0 mg.
Cholesterol	0
Weight 14 Gm.	Calories 126

Total unsaturated Fatty Acids—85%

TYPICAL AMOUNTS PER DIET

For a 3600 calorie diet	3 Tbsp.
For a 3000 calorie diet	2.5 Tbsp.
For a 2000 calorie diet	1.5 Tbsp.

make poor eaters want to

"COME AND GET IT"

REDISOL®

CYANOCOBALAMIN (CRYSTALLINE VITAMIN B_{12})

REDISOL—vitamin B_{12}—used as a dietary supplement often stimulates appetite with consequent weight gain—youngsters look forward to their meals again.

Cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) and soluble REDISOL Tablets (25, 50, 100, 250 mcg.) mix readily with liquids.

MSD **MERCK SHARP & DOHME**
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

Redisol is a trade-mark of Merck & Co., Inc.

FEWER ANGINAL ATTACKS. PROTECTS AGAINST PAIN AND CONTROLS ANXIETY. (EQUANIL® AND PETN)

Meprobamate, Wyeth

EQUANITRATE*

*Trademark

Meprobamate and Pentaerythritol Tetranitrate

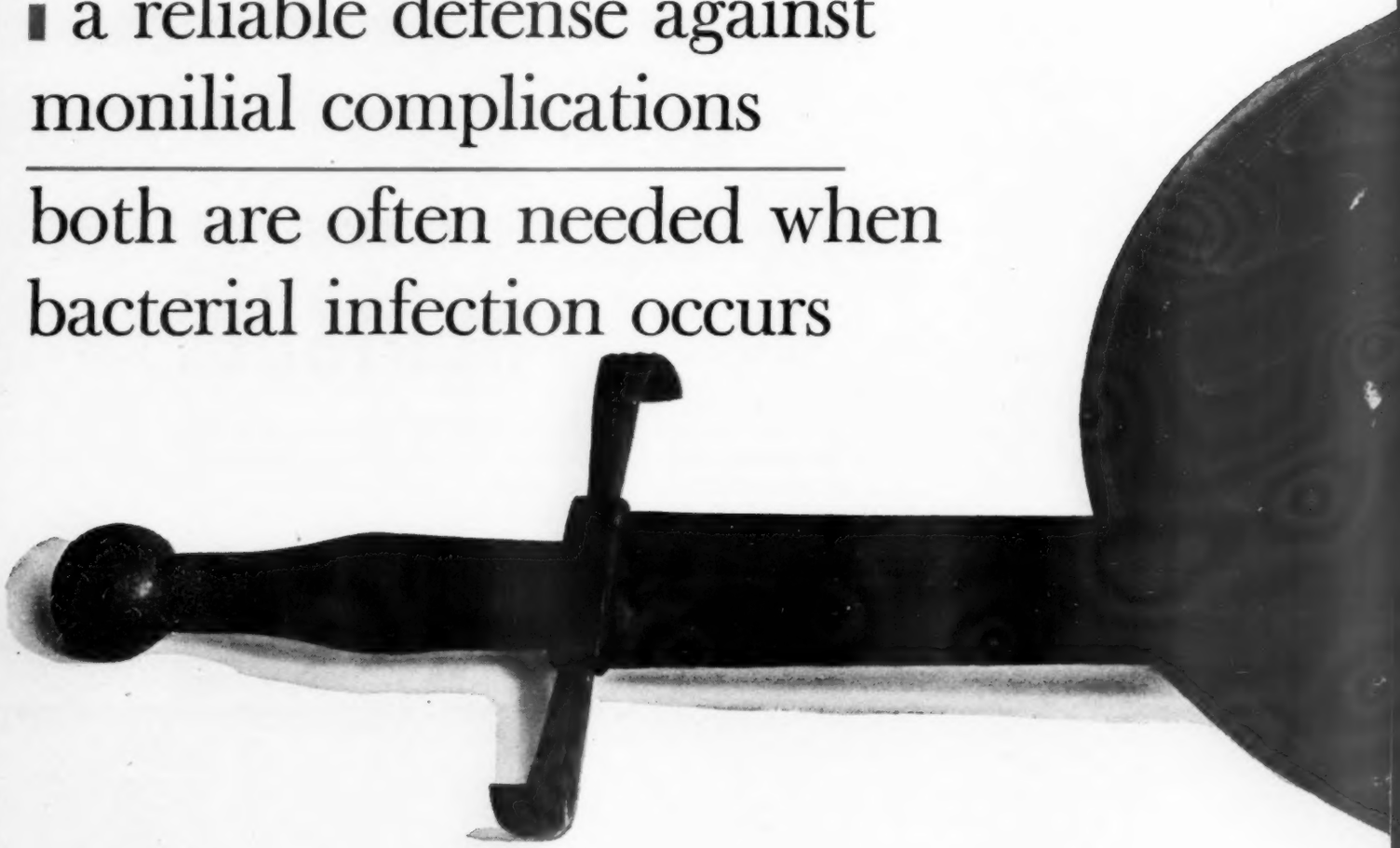
Wyeth®

Tablets, vials of 50, meprobamate (200 mg.) and pentaerythritol tetranitrate (10 mg.)

▮ prompt, aggressive antibiotic action

▮ a reliable defense against monilial complications

both are often needed when bacterial infection occurs



for a direct strike at infection Mysteclin-V contains tetracycline phosphate complex

It provides a direct strike at all tetracycline-susceptible organisms (most pathogenic bacteria, certain rickettsias, certain large viruses, and Endamoeba histolytica).

It provides the new chemical form of the world's most widely prescribed broad spectrum antibiotic.

It provides unsurpassed initial blood levels—higher and faster than older forms of tetracycline—for the most rapid transport of the antibiotic to the site of infection.

SQUIBB

CENTENNIAL 1858 III 1958 SQUIBB

Squibb Quality—the Priceless Ingredient

Capsules *(250 mg./250,000 u.),*
bottles of 16 and 100.
Half-strength Capsules *(125 mg./125,000 u.),*
bottles of 16 and 100.
Suspension *(125 mg./125,000 u. per 5 cc.)*
60 cc. bottles.
Pediatric Drops *(100 mg./100,000 u. per cc.).*
10 cc. dropper bottles.

for protection against monilial complications

Mysteclin-V contains Mycostatin

It provides the antifungal antibiotic, first tested and clinically confirmed by Squibb, with specific action against Candida (Monilia) albicans.

It acts to prevent the monilial overgrowth which frequently occurs whenever tetracycline or any other broad spectrum antibiotic is used.

It protects your patient against antibiotic-induced intestinal moniliasis and its complications, including vaginal and anogenital moniliasis, even potentially fatal systemic moniliasis.

MYSTECLIN-V

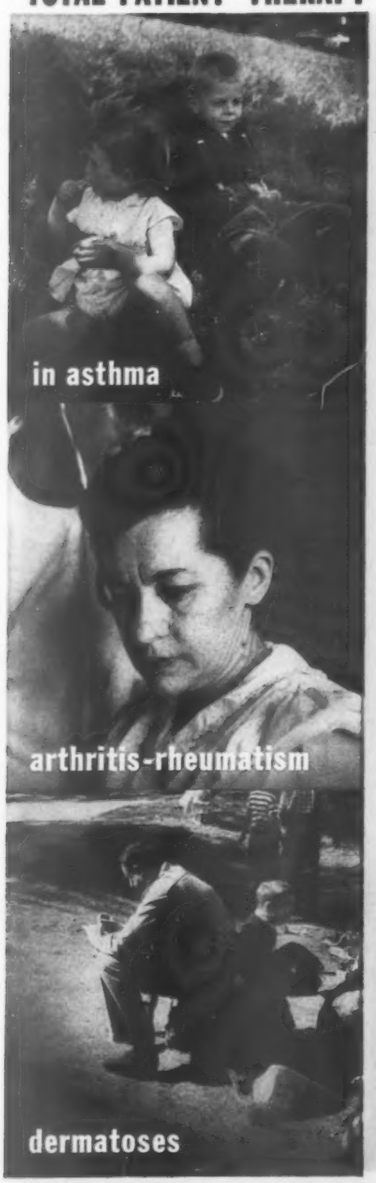
Squibb Tetracycline Phosphate Complex (Sumycin) and Nystatin (Mycostatin)

MORE EFFICIENT THAN PREDNI-STEROIDS ALONE

ATARAXOID®

prednisolone-hydroxyzine

'TOTAL PATIENT' THERAPY



EFFECTIVELY CONTROLS anxiety-tension-induced exacerbations and emotional factors through the safe tranquilizer and muscle-relaxant[1] effects of hydroxyzine. Potentiates the action of prednisolone, markedly improving degree of response, sometimes doubling dosage efficiency, and permitting lower dosages.[2-4] The unique anti-secretory action[5] of hydroxyzine also minimizes corticoid-induced gastric reactions.

1. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind.
2. Johnston, T. G., and Casert, A. G.: Clin. Rev. 1:17, 1958.
3. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957.
4. Individual Case Reports to Medical Dept., Pfizer Laboratories.
5. Strub, I. H.: To be published.

SUPPLIED:

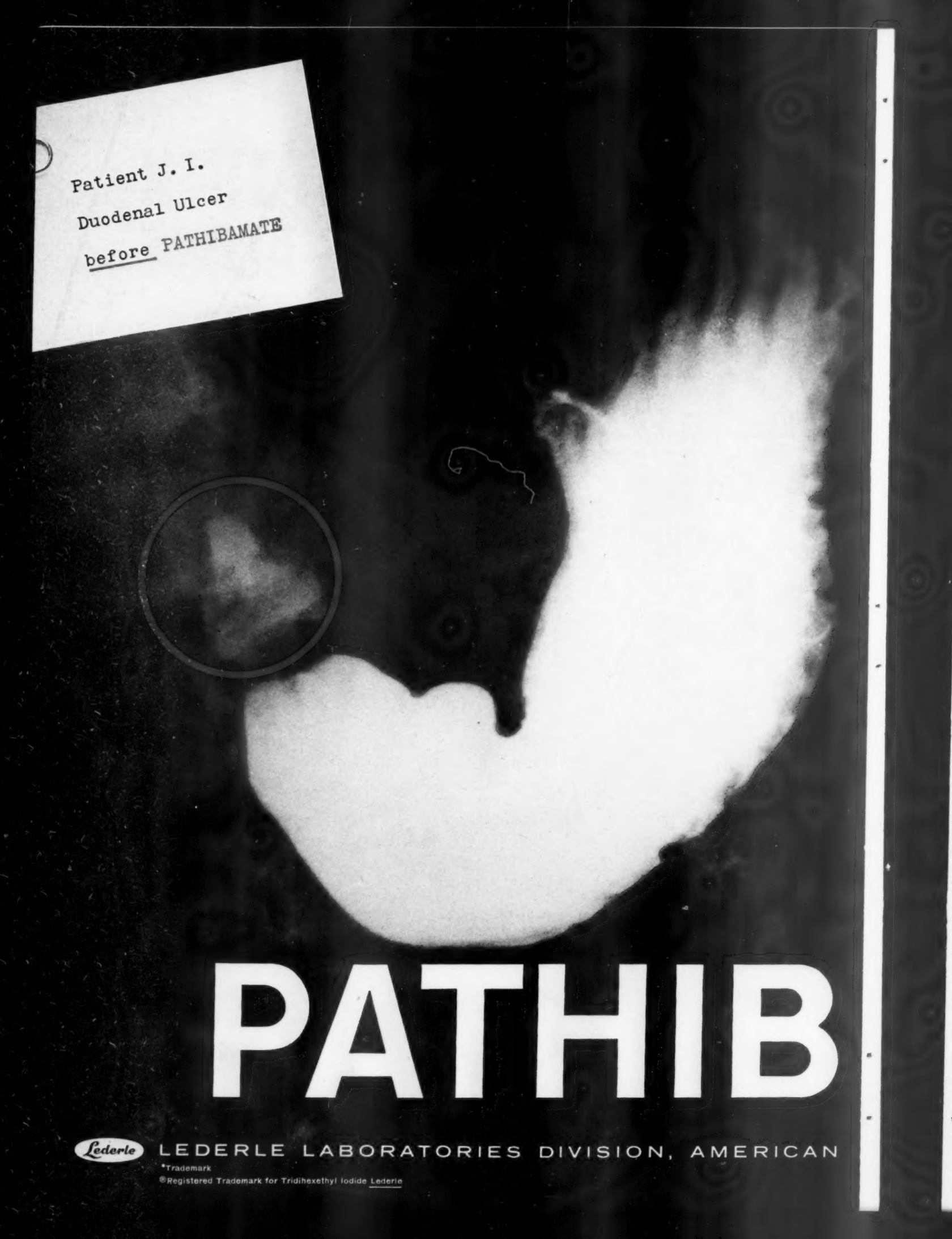
ATARAXOID *1.0*
scored green tablets, 5.0 mg. prednisolone and 10 mg. hydroxyzine hydrochloride, bottles of 30 and 100.

ATARAXOID *2.5*
scored blue tablets, 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride, bottles of 30 and 100.

ATARAXOID *5.0*
scored orchid tablets, 1.0 mg. prednisolone and 10 mg. hydroxyzine hydrochloride, bottles of 100.

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York



PATHIB

Lederle LEDERLE LABORATORIES DIVISION, AMERICAN

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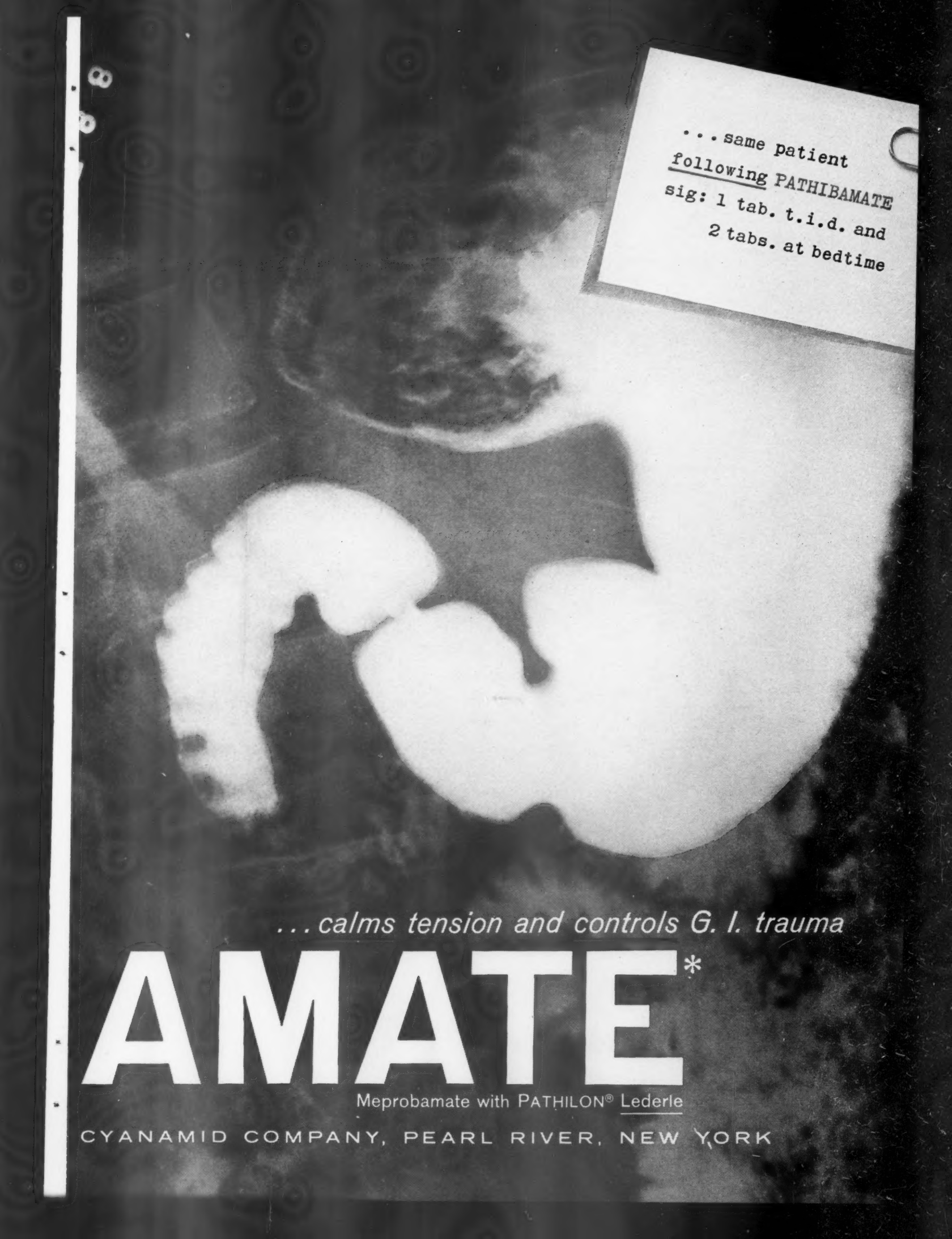
®Registered Trademark for Tridihexethyl Iodide Lederle


. . . same patient
following PATHIBAMATE
sig: 1 tab. t.i.d. and
2 tabs. at bedtime
. . . calms tension and controls G. I. trauma
AMATE*
Meprobamate with PATHILON® Lederle
CYANAMID COMPANY, PEARL RIVER, NEW YORK

dual control in a single tablet

when asthma is complicated by "hay fever"

You can relieve the symptoms of both asthma and pollinosis simultaneously with new TEDRAL ANTI-H.

Tedral anti-H combines Tedral, the *accepted* antiasthmatic, with antihistaminic chlorpheniramine to

- *relieve constriction, reduce congestion and allay apprehension in asthma, and*
- *alleviate the distressing symptoms of "hay fever" and nonseasonal upper respiratory allergies.*

dosage: *1 or 2 tablets every 4 hours*

new

Tedral® anti-H

antiasthmatic / antihistaminic

WARNER-CHILCOTT

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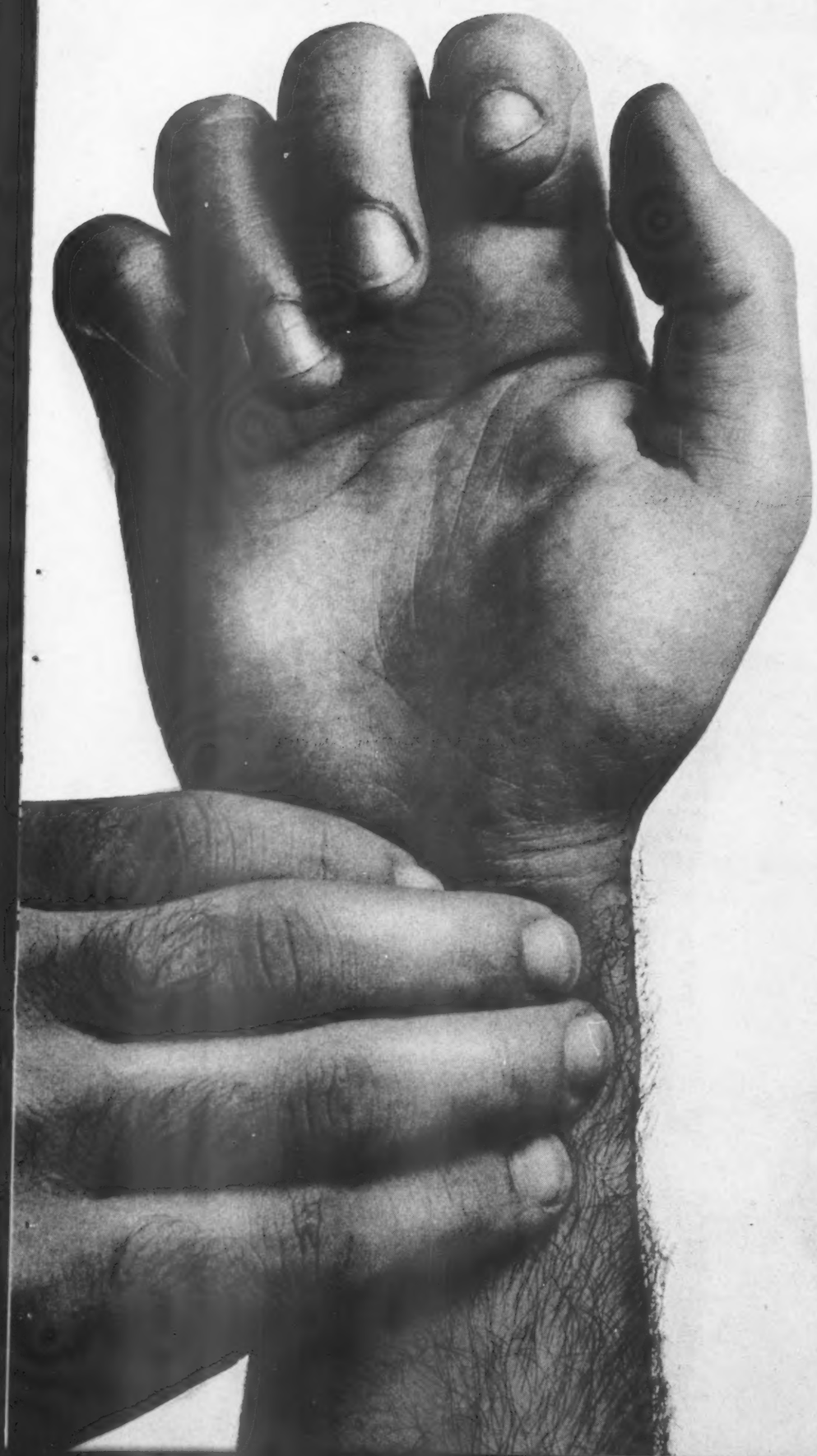


pulse rate up?

Serpasil slows heart rate in most cases of organic or functional tachycardia.

You'll find it especially valuable in cardiac patients whose conditions are aggravated by heart speed-up. Through a unique heart-slowing action, independent of its antihypertensive effect, Serpasil prolongs diastole and allows more time for the myocardium to rest. Blood flow and cardiac efficiency are thereby enhanced.

What's more, you can prescribe Serpasil with confidence. Therapy with Serpasil is virtually free of the dangers (heart block and cardiac arrest) heretofore encountered with heart-slowing drugs. Side effects are generally mild and can be overcome by adjusting dosage.

DOSAGE FOR TACHYCARDIA
Dose range is 0.1 to 0.5 mg. (two 0.25-mg. tablets) per day conveniently taken in a single dose. Rapid heart rate usually will be relieved within 1 to 2 weeks, at which time the daily dose should be reduced. Suppression of tachycardia often persists after therapy is stopped.

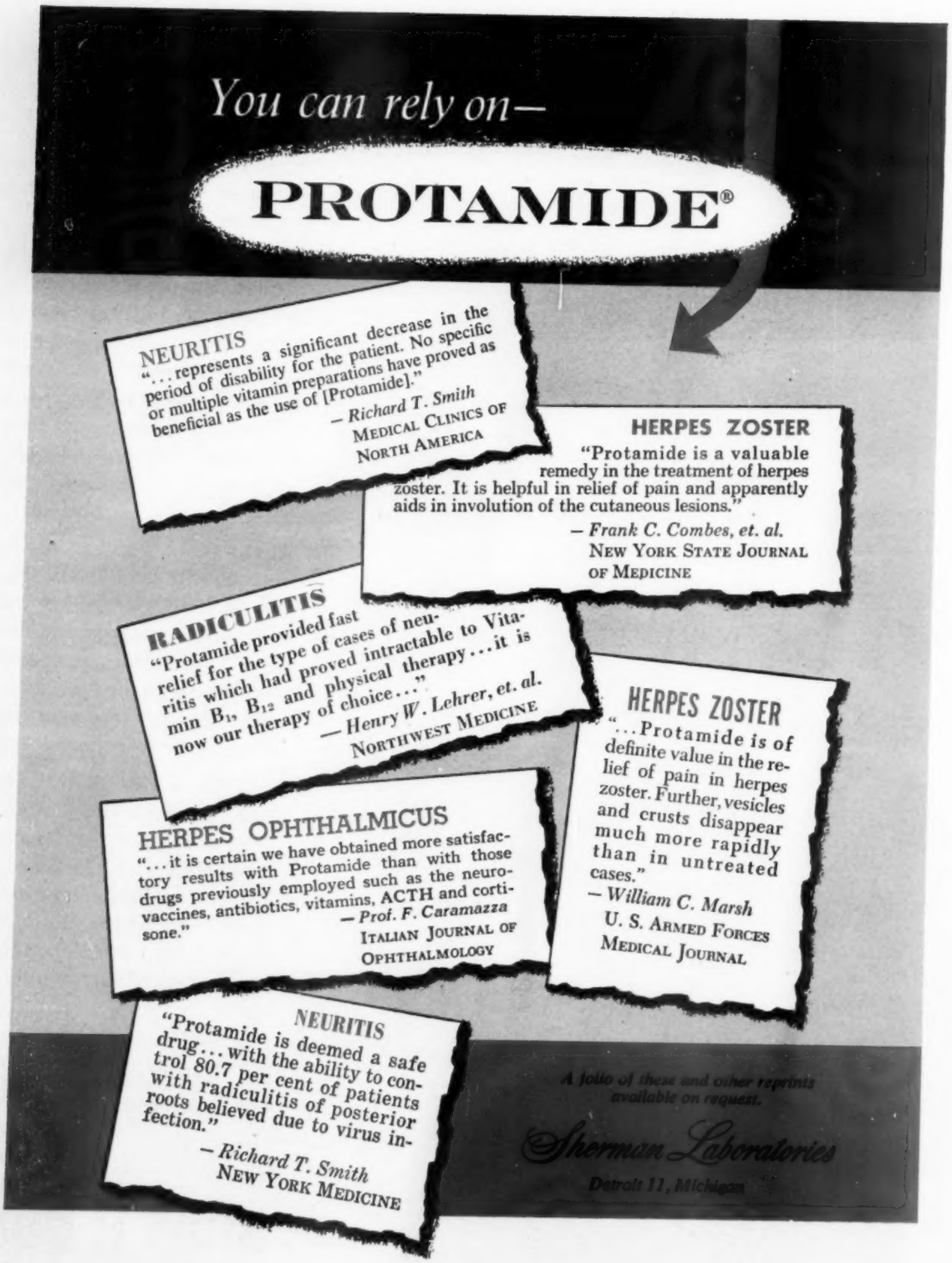
NOTE: In patients receiving digitalis or quinidine, Serpasil therapy should be initiated with especially careful observation. Serpasil is not recommended in cases of aortic insufficiency.

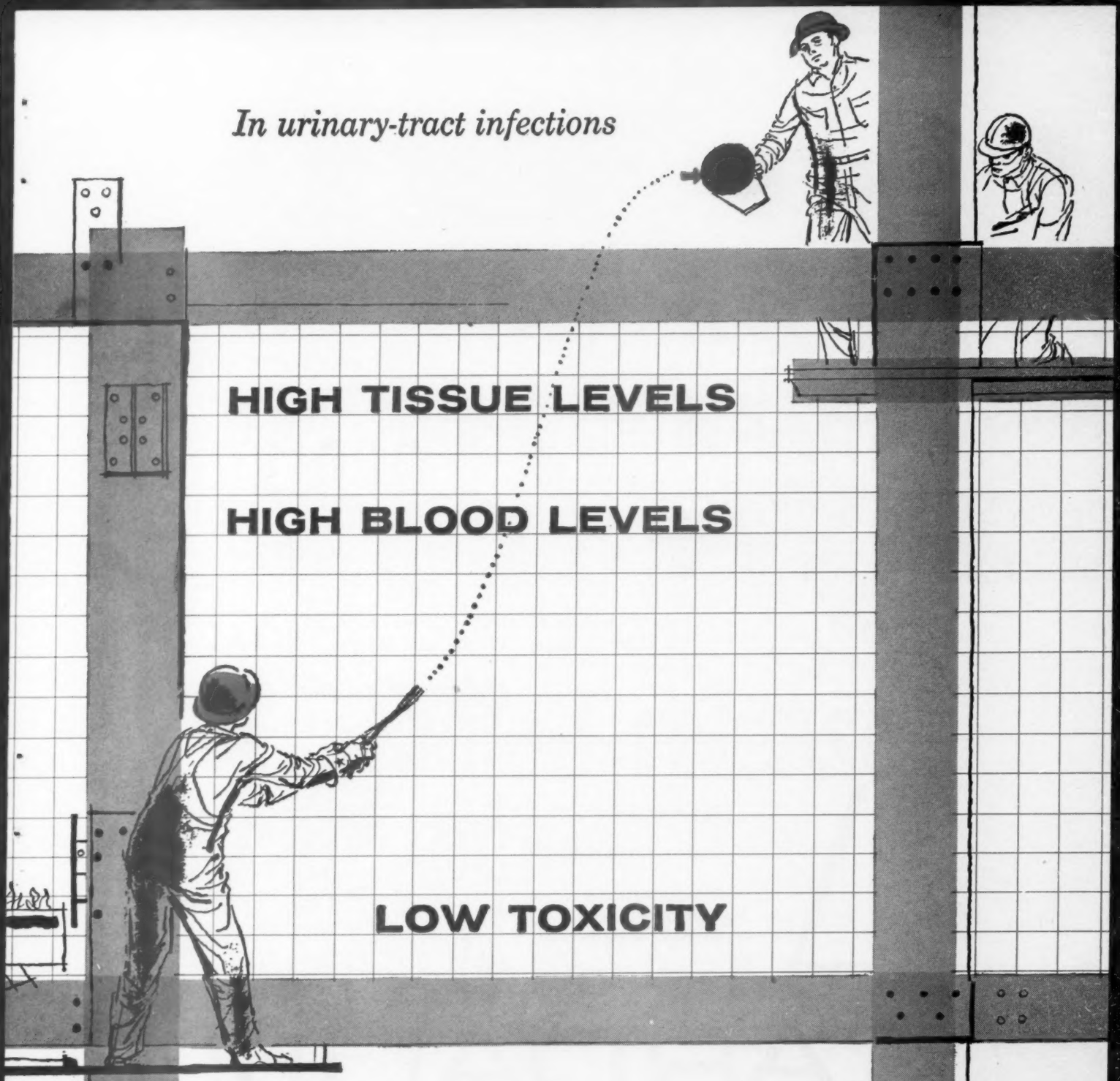
SUPPLIED: *Tablets*, 1 mg. (scored), 0.25 mg. (scored) and 0.1 mg. *Elixirs*, 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon.

slow it down with Serpasil®

(reserpine CIBA)

2/2588MB


You can rely on—
PROTAMIDE®
NEURITIS
"... represents a significant decrease in the period of disability for the patient. No specific or multiple vitamin preparations have proved as beneficial as the use of [Protamide]."
— Richard T. Smith
MEDICAL CLINICS OF NORTH AMERICA
HERPES ZOSTER
"Protamide is a valuable remedy in the treatment of herpes zoster. It is helpful in relief of pain and apparently aids in involution of the cutaneous lesions."
— Frank C. Combes, et. al.
NEW YORK STATE JOURNAL OF MEDICINE
RADICULITIS
"Protamide provided fast relief for the type of cases of neuritis which had proved intractable to Vitamin B1, B12 and physical therapy... it is now our therapy of choice..."
— Henry W. Lehrer, et. al.
NORTHWEST MEDICINE
HERPES OPHTHALMICUS
"... it is certain we have obtained more satisfactory results with Protamide than with those drugs previously employed such as the neurovaccines, antibiotics, vitamins, ACTH and cortisone."
— Prof. F. Caramazza
ITALIAN JOURNAL OF OPHTHALMOLOGY
HERPES ZOSTER
"... Protamide is of definite value in the relief of pain in herpes zoster. Further, vesicles and crusts disappear much more rapidly than in untreated cases."
— William C. Marsh
U. S. ARMED FORCES MEDICAL JOURNAL
NEURITIS
"Protamide is deemed a safe drug... with the ability to control 80.7 per cent of patients with radiculitis of posterior roots believed due to virus infection."
— Richard T. Smith
NEW YORK MEDICINE
A folio of these and other reprints available on request.
Sherman Laboratories
Detroit 11, Michigan



SUSPENSION TABLETS

SULFOSE®

Triple Sulfonamides, Wyeth

(*Trisulfapyrimidines: Sulfadiazine, Sulfamerazine, Sulfamethazine*)

PHYSICIANS' COUNCIL · INFORMATION ON CHILD HEALTH ·

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

Wyeth®

Philadelphia 1, Pa.

make poor eaters want to

"COME AND GET IT"

REDISOL®

CYANOCOBALAMIN (CRYSTALLINE VITAMIN B_{12})

REDISOL—vitamin B_{12}—used as a dietary supplement often stimulates appetite with consequent weight gain—youngsters look forward to their meals again.

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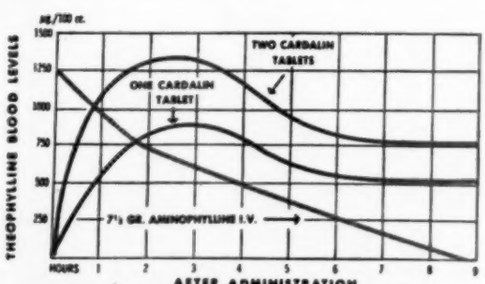

(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11:301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100:309, 1950.)

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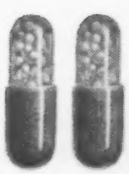
q. 12 h. 

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1. Meprobamate is more widely prescribed than any other tranquilizer. Source: Independent research organization; name on request.
2. Baird, H. W., III: A comparison of Meprospan (sustained action meprobamate capsule) with other tranquilizing and relaxing agents in children. Submitted for publication, 1958.

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*Oettinger, L., Jr.: The Use of Deanol (Deaner) in the Treatment of Disorders of Behavior in Children. Presented before the American Encephalographic Society Meeting, Atlantic City, June 14, 1958. To be published, Journal of Pediatrics.

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1. Lewis, J.M., et al.: J. Pediat. 31:496.

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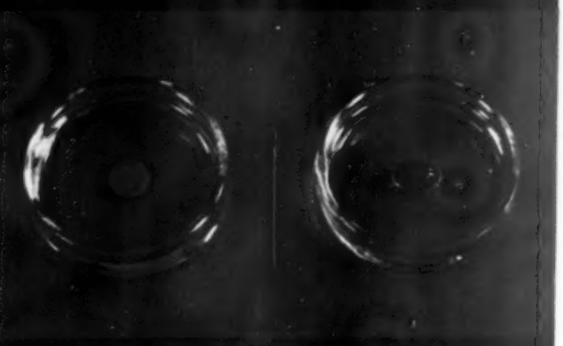

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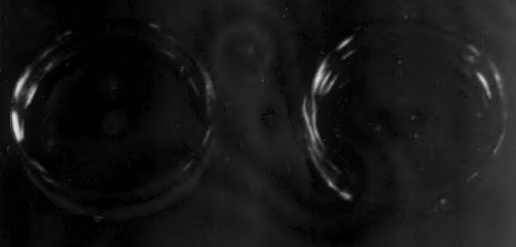

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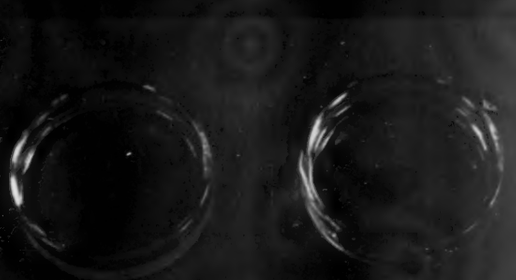

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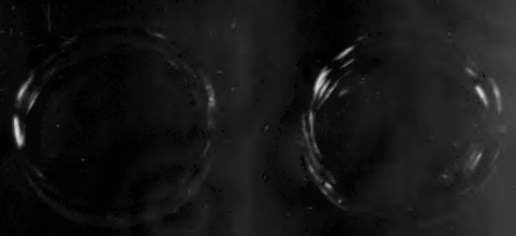

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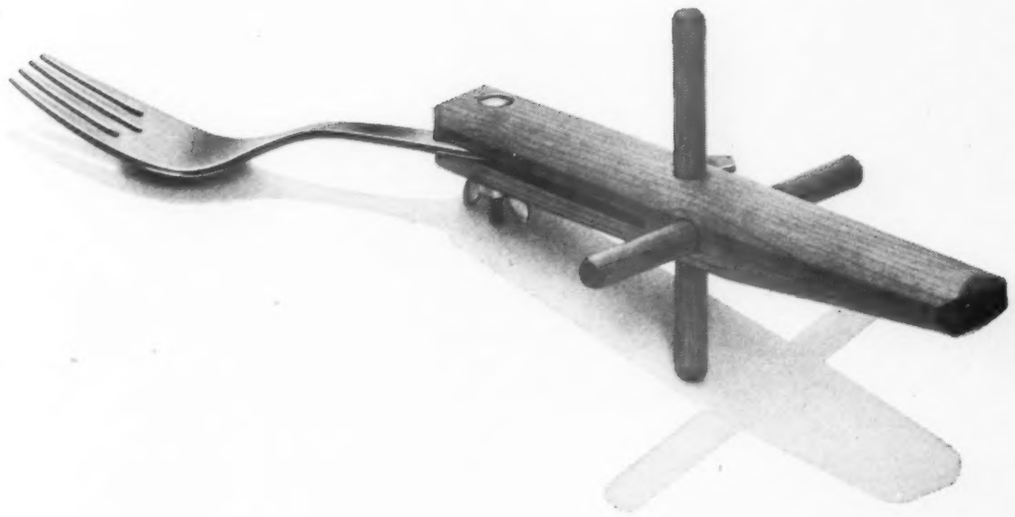

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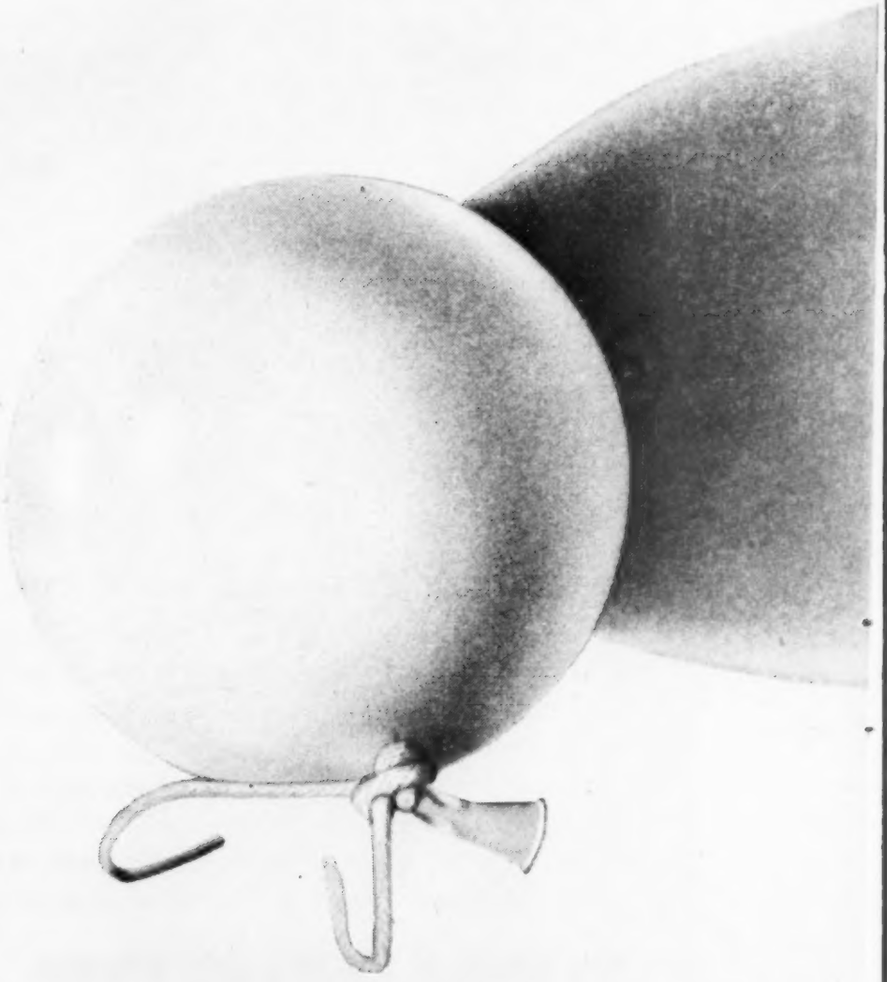

"Ninety to 95 per cent of all urologic disturbances in patients of all ages are the result of obstruction and/or infection, urinary blockage and stasis being the fundamental predisposing etiology in nearly all cases of urinary tract infection."[1]

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"Nitrofurantoin [FURADANTIN] may be used for protracted periods for the suppression of infection in the urinary tract, even in the presence of probable obstruction . . . it may provide prolonged relief from symptoms and permit better selection of the proper time for surgical or manipulative procedures."[3]

AVERAGE ADULT FURADANTIN DOSAGE: 100 mg. q.i.d. with meals and with food or milk on retiring. SUPPLIED: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.; Intravenous Solution, 60 mg. per 10 cc. ampule.

REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957, p. 101. 2. Carroll, G.: Bacterial Infections of the Urinary Tract (Male), in Conn, F.: Current Therapy 1956, Philadelphia, W. B. Saunders Co., 1956, p. 301. 3. Jawetz, E.: A.M.A. Arch. Int. M. 100:549, 1957.

NITROFURANS—a *new* class of antimicrobials—neither antibiotics nor sulfonamides

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A new concept in antihypertensive therapy: concomitant use of an improved ganglionic blocking agent ['Inversine'] and a new antihypertensive agent ['Diuril'] for smoother, simplified management of hypertension.

Longer Life for Hypertensives

In moderate, severe, and malignant hypertension, ganglionic blocking 'Inversine' often makes possible a lessening of cardiovascular-renal damage, regression of the basic disease, and prolongation of life.

"When employed under carefully controlled conditions with adequate attention to proper regulation of dosage, mecamylamine ['Inversine'] may be expected to reduce blood pressure effectively and to ameliorate various manifestations of hypertensive-cardiovascular disease. These include such symptoms as headache, dizziness, vertigo, hypertensive encephalopathy, cerebral or subarachnoid hemorrhage, retinopathy, cardiac hypertrophy and, in some cases, cardiac decompensation."

Council on Drugs, New and Nonofficial Remedies: Philadelphia, J. B. Lippincott Co., 1958, p. 285.

Now, concomitant use of a newly discovered antihypertensive agent ['Diuril' (Chlorothiazide)] has been found to enhance the hypotensive effect of 'Inversine'—while reducing the required dosage of 'Inversine' and often minimizing the serious side effects of ganglionic blockade.

'Inversine'
MECAMYLAMINE HYDROCHLORIDE

a greatly improved ganglionic blocking agent

Unlike the other ganglionic blocking agents, 'Inversine' is not a quaternary ammonium compound. It is a secondary amine, and has significant advantages over all other ganglionic blocking drugs:

- of the orally effective blocking agents, only 'Inversine' is completely and uniformly absorbed
- it provides predictable, reproducible effects with minimal day-to-day fluctuations in blood pressure response
- 'Inversine' is effective in low dosage
- permits convenient dosage schedules
- usefulness not limited by development of tolerance
- it has a gradual onset of effect, reducing the likelihood of sudden drops in blood pressure

'Diuril'
CHLOROTHIAZIDE

new and unique antihypertensive agent

- provides basic therapy to improve and simplify the management of hypertension
- markedly enhances the effects of other antihypertensive agents
- often reduces dosage requirement of ganglionic blocking agents and other antihypertensive agents below the level of serious side effects
- smooths out blood pressure fluctuations
- added to other antihypertensive agents, is often effective in controlling blood pressure of even highly resistant cases
- effectiveness not diminished by development of tolerance
- well tolerated even at maximum therapeutic doses

DOSAGE RECOMMENDATIONS

New Patients

1. *Initiate therapy with 'Diuril'*
'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. *Adjust dosage of other agents*
The dosage of other antihypertensive medication ('Inversine', reserpine, veratrum, hydralazine, etc.) is adjusted as indicated by patient response.

'Inversine' is given in the same manner whether used with 'Diuril' or alone. Recommended initial dosage is 2.5 mg. twice a day, preferably after meals. May be increased by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'Inversine' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

3. *Adjust dosage of all medication*
The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

Patients on 'Inversine' and/or other ganglionic blocking agents

1. *Initiate therapy with 'Diuril'*
'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. *Adjust dosage of ganglionic blocking agent*
If the patient is established on a ganglionic blocking agent (e.g., 'Inversine') it should be continued, but the total daily dosage should *immediately* be reduced by as much as 25 to 50 per cent. This will reduce the serious side effects often observed with ganglionic blockade.

If other antihypertensive agents are used, their dosage should be adjusted as indicated by patient response.

3. *Adjust dosage of all medication*
The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

Precautions: Side effects of 'Inversine' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'Inversine' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction.

Supplied: 'Inversine', tablets of 2.5 mg. and 10 mg. Bottles of 100. 'Diuril', tablets of 250 mg. and 500 mg. Bottles of 100 and 1000.

Inversine
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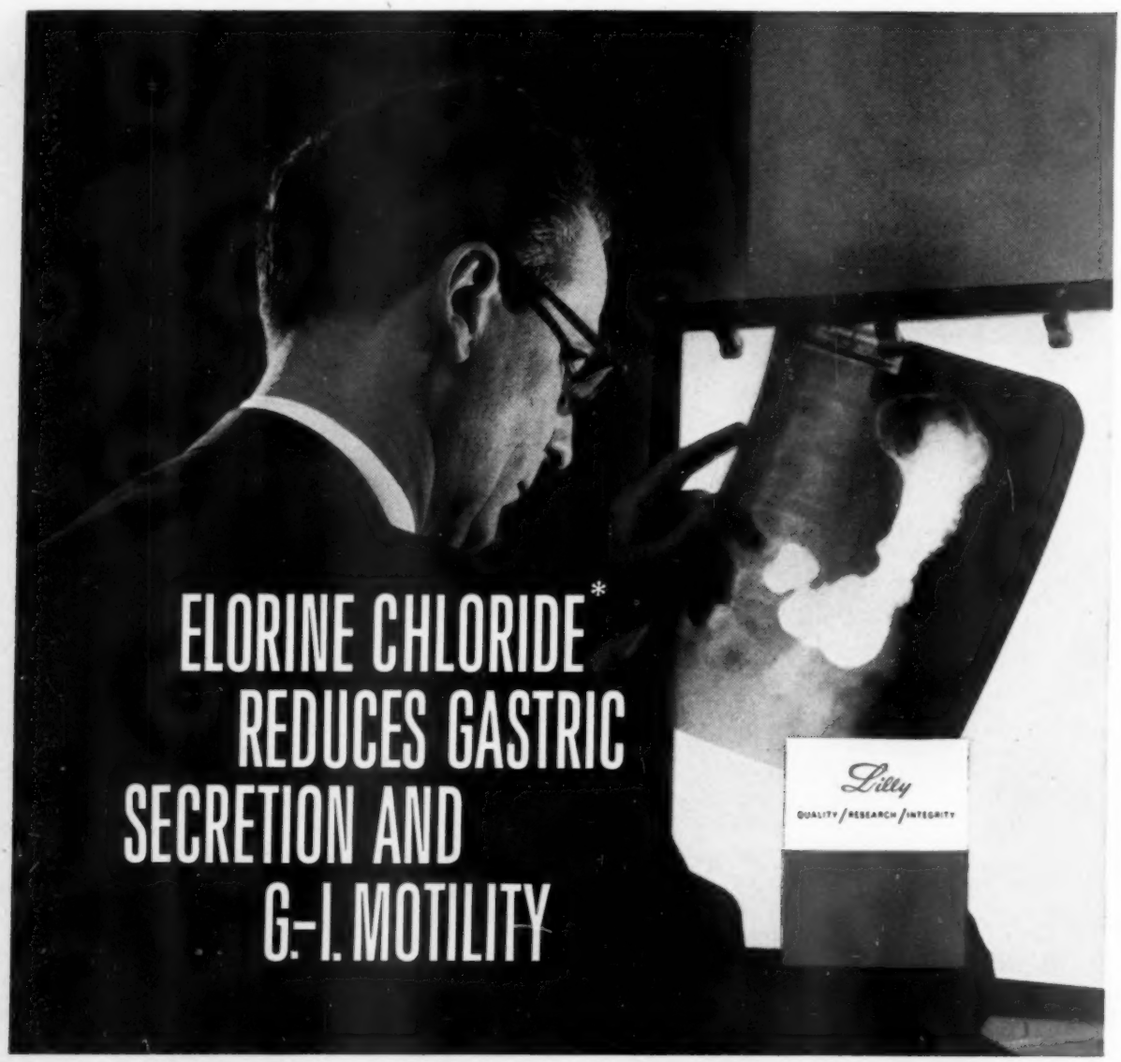

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Dosage should be tailored to patient tolerance. In peptic ulcer, the average adult dose ranges from 100 to 250 mg. three or four times daily. 'Elorine Chloride' is available in pulvules of 50 and 100 mg.

*'Elorine Chloride' (Tricyclamol Chloride, Lilly)

1. Sun, D. C. H., and Shay, H.: A.M.A. Arch. Int. Med., *97*:442, 1956.

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The American Journal of Medicine

VOL. XXV OCTOBER, 1958 NO. 4

Editorial

Re-examination of Salt and Water Retention in Congestive Heart Failure*

Significance of Renal Filtration Fraction

SINCE the work of Starr [*1*] who concluded that the increase in venous pressure observed in congestive heart failure is due to an increased plasma volume, the "forward" theory of heart failure has been the subject of much research attempting to describe the precise mechanisms by which the extracellular volume is expanded during cardiac decompensation. Warren and Stead [*2*] emphasized the diminished renal excretion of sodium and water as the cause of fluid retention in patients in whom edema forms. The cause of this renal salt and water retention was investigated by Merrill [*3*], who found that in patients in severe cardiac failure, filtration rates were reduced to one-third or one-half of normal, and renal blood flow was reduced to an even greater degree. Similar decreases in glomerular filtration rate had been observed by Seymour et al. [*4*], and Merrill theorized that renal ischemia leads to a decreased glomerular filtrate which is almost completely reabsorbed by normally functioning transport systems. Decreases in glomerular filtration rate (GFR) and renal blood flow (RBF) have been confirmed by numerous investigators [*5–9*].

However, much evidence has been reported which does not substantiate this theory: (1) Cases of cardiac failure in man have been reported in which GFR is within normal limits [*10–12*]. (2) Diuresis (spontaneous or induced by bedrest or therapeutics other than diuretics) occurring in cardiac compensation is often not accompanied by an increase in glomerular filtration rate [*4,10,12,13*]. (3) Renal retention of salt in experimental heart failure in the dog takes place before any decrease in filtration rate is observed and may continue for long periods of time without any reduction in filtration rate [*14–16*].

These experiments demonstrated that the decreased renal sodium and water excretion in heart failure showed no constant relationship to filtered load. Moreover, since the clinical symptoms of heart failure (edema, venous distention, basilar pulmonary rales, etc.) are quite gross, the work on experimental animals indicates that the earliest stages of salt retention in most patients may occur before any decrease in filtration rate. It seemed evident, therefore, that the primary cause of salt retention was an increased tubular reabsorption of electrolytes and water. It has been shown that in patients with congestive heart failure and edema, the production as well as excretion of aldosterone are much greater than normal [*17–20*]. On the basis of these observations it is concluded that

* This work was supported by the American Heart Association, TJ56-198; the Life Insurance Medical Research Fund, G-57-46; the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service, A-1740; and a teaching grant from the U.S. Atomic Energy Commission, BM-2-58A.

increased tubular reabsorption as a result of increased aldosterone production is the mechanism of salt retention in congestive failure before there is any change in GFR. The stimulus for this increased aldosterone production is believed to occur by way of an arterial receptor mechanism which is triggered by a decreased *effective* blood volume [*21*].

It should be noted, however, that these increased aldosterone levels have been demonstrated in patients or dogs with fully developed congestive failure, rather than in those with the early, clinically undetectable stages of the disease during which the onset of salt retention is occurring. It has also been shown that in compensated patients urinary levels of aldosterone still remain pathologically elevated, although somewhat diminished from former levels [*22,23*], i.e., diuresis and sodium balance can be affected by "standard therapeutic measures" (Gordon gives no other details) in the presence of large quantities of aldosterone. Moreover, in patients suffering from primary aldosteronism [*24*] polyuria is present, as contrasted with the water retention in patients with congestive heart failure. The following explanation has been offered by Johnson and Conn [*21*]: The pitressin resistant polyuria of primary aldosteronism is due to effects of chronic potassium deficiency produced by the aldosterone. "The rarity of kaliopenia in congestive heart failure with secondary aldosteronism may be due to the inability to increase the GFR. A load of sodium sufficiently large to bring about potassium depletion never reaches the distal tubule for exchange with potassium." This explanation meets with the same difficulties described in the first section, i.e., it cannot account for the cases in which a normal GFR is present, since in these patients and dogs, ample amounts of sodium would reach the distal tubule. The most damaging evidence against aldosterone being primarily responsible for salt retention is the work of Davis, Howell and Hyatt [*15*], who performed adrenalectomy in eight dogs, allowed a control period during recovery, and then induced a progressive cardiac failure by partial ligation of the pulmonary artery. During the control period, the dogs were maintained in sodium balance by administration of 3 mg./day DCA (25 mg./day cortisone was given throughout the experiments). After partial pulmonary artery ligation and the development of clinical signs of cardiac failure it was found that GFR had decreased in only four of the eight dogs. Yet all eight dogs exhibited salt retention on a dosage of only 1 mg./day DCA, whereas, as already mentioned, 3 mg./day DCA was required for salt balance before cardiac failure was induced. This retention ranged from 50 to 80 per cent of the salt intake. If administration of DCA was discontinued, diuresis occurred, indicating that a small amount of hormone was necessary for retention to occur. If the dose of DCA given was increased from 1 to 25 mg./day the retention grew progressively greater, becoming almost complete at very high dosage levels, indicating that the increased aldosterone found in congestive failure certainly increases salt retention. However, these experiments demonstrate clearly that salt retention would still occur even in the presence of reduced amounts of hormone, and that aldosterone is not the primary or initiating factor. Since GFR was normal in half the animals, the conclusion must be drawn that the primary cause of salt retention in congestive heart failure is an increased tubular reabsorption of electrolyte and water which is not dependent on adrenal hormones. We believe this factor to be the presence of an increased renal filtration fraction.

FILTRATION FRACTION IN CONGESTIVE HEART FAILURE

It is generally accepted that approximately 85 per cent of filtered sodium is reabsorbed actively in the proximal tubule, followed by the passive reabsorption of an equivalent amount of water necessary to maintain isotonicity within the tubule. Almost all the remaining sodium is then actively reabsorbed in the distal tubule possibly under the influence of aldosterone, water most likely following passively in the presence of ADH. On the basis of these physiologic mechanisms, a decreased excretion of sodium chloride could be explained only by a decreased filtered load or by increased enzyme activity, usually presumed to be caused by aldosterone. Within the past year a new method called "stop flow" analysis [*25–27*], developed in our laboratory, has made possible a practical and easily applied procedure for the direct localization and quantification of function of the various nephron segments. Using this procedure, it was found that during the infusion of a strong osmotic diuretic (mannitol), the sodium concentration of the fluid reabsorbed from the proximal tubule remained identical with that of plasma, i.e., the proximal tubule was unable to lower sodium concentration even in

the presence of large amounts of an osmotic diuretic. These and other experiments, and the conclusions drawn from them are described in detail elsewhere [*28*]. We have been led to believe that both water and sodium reabsorption by the proximal tubule is a passive process, mediated through the colloid osmotic pressure within the peritubular capillaries. Since the hydrostatic pressures within the peritubular capillaries and the proximal tubular lumens are equal, as shown by Wirz [*29*] and by Gottschalk and Mylle [*30*], the plasma protein within the capillaries exerts an osmotic force favoring water reabsorption, which is not offset by any opposite force within the tubule (essentially no protein is filtered through the glomerulus). Sodium, concentrated by the reabsorption of water, then moves passively to maintain isotonicity. In such a system filtration fraction would become of major importance in determining this colloid osmotic pressure (COP). Under normal conditions one-fifth of the renal plasma flow is filtered at the glomerulus (filtration fraction = 0.2), increasing the protein concentration of the plasma which then flows into the efferent arteriole. For example, the normal plasma COP of 25 mm. Hg would be elevated to 31 mm. Hg after filtration had occurred. This would then be the effective pressure causing proximal reabsorption of water and sodium. Consider now a situation in which the glomerular filtrate was 40 per cent of the renal plasma flow, i.e., the filtration fraction rose to 0.4. The COP would now be changed from 25 to 42 mm. Hg after filtration, thus promoting increased proximal reabsorption. This view is substantiated by the work of Vogel [*31,32*] who showed that infusion of colloid into the renal portal system of the frog greatly decreased the excretion of water and electrolytes without affecting GFR. This also explains the results of Elkinton and co-workers [*33*], and Selkurt [*34*] who reported that acute reductions in renal blood flow (accomplished by administration of neosynephrine and aortic narrowing, respectively), not sufficient to cause reduction in GFR, resulted in reductions of sodium excretion, from 0.336 to 0.200 mEq./minute in the latter paper. Conversely, the former workers reported that increasing RBF without changing GFR resulted in increased sodium excretion. Similar results have been obtained by Shipley and Study [*35*], who increased RBF by increasing renal arterial blood pressure and found an increase in urine flow but no change in GFR. A more detailed study of the literature has been described previously [*28*].

The ability of the kidney to stabilize GFR in the presence of a wide range of RBF is one of the major features of renal hemodynamics. Even when GFR is changed by large increases or decreases in RBF, the GFR changes are much less than the changes in RBF [*36*], i.e., the poorly understood phenomenon of "auto-regulation" maintains GFR by changing filtration fraction.

The existence of this mechanism in congestive heart failure is readily apparent. Even in those patients with reduced GFR [*3–9*] the RBF, when measured, was always found to be reduced to a much greater extent, resulting in an increased filtration fraction. The important question, however, was whether or not such a mechanism could explain the cases reported earlier in which compensation or decompensation occurred without any change in filtration rate.

Cardiac Failure in Man in Whom GFR is within Normal Limits. Heller and Jacobson [*10*] studied patients in the edematous state and found filtration rates as high as 105 ml./minute, but the lowest filtration fraction was 0.323, the average being 0.405 ± 0.083, as compared to a normal average of 0.174 ± 0.023. Davis and Shock [*11*] found normal filtration rates in four patients in congestive failure. All had very reduced RBF, with filtration fractions from 0.60 to 0.38. Sinclair-Smith et al. [*12*] followed a cardiac patient as decompensation occurred. There was no change in GFR but RBF was greatly reduced, raising filtration fraction to 0.49 from the value of 0.23 during the previous period of compensation.

The Occurrence of Compensation Not Accompanied by an Increase in GFR. Seymour and his colleagues [*4*] actually found slight decreases in GFR during compensation in two patients. In both cases, RBF showed approximately 50 per cent increases, resulting in a lowering of filtration fraction to 0.38 and 0.30 from previous values of 0.74 and 0.48. It is of interest to note that the patient with the filtration fraction of 0.74 had a normal GFR while in severe congestive failure. Heller and Jacobson [*10*] effected compensation in patients by digitalis, bedrest and salt restriction. Filtration rate increased in only two of four patients, but RBF increased in all, resulting in a reduction of the average filtration rate from 0.48 to 0.32. Sinclair-Smith et al. [*12*] effected recovery in a patient by the use of digitalis. GFR did not change but RBF

greatly increased, lessening filtration fraction from 0.54 to 0.23 at the end of compensation. Brod and Fejfar [*13*] studied nineteen patients, in various states of heart failure, at night during spontaneous diuresis. They reported variable changes in GFR, often showing only very slight rises, which in their opinion could not explain the magnitude of the diuresis. However, in every case, diuresis was accompanied by a large increase in RBF and a fall in filtration fraction.

Renal Retention of Salt in Experimental Heart Failure with No Change in GFR. Barger, Rudolph and Yates [*14*] observed that in dogs with surgically created valvular lesions of the heart, the salt retention which occurred during the early stages of failure was not accompanied by any decrease in GFR. However, all dogs showed markedly decreased RBF with filtration fractions up to 0.4. As discussed earlier, only one-half of the adrenalectomized dogs of Davis, Howell and Hyatt [*15*] showed a decrease in GFR during the onset of failure resulting from partial pulmonary artery ligation. RBF decreased and filtration fraction rose in seven of eight dogs (no specific excretory data are given for dog number 8). It is also significant that only one dog responded to the administration of digoxin. Only in this dog did administration of the drug cause improvement in "renal circulation" (no figures given), resulting in a natriuresis which occurred in spite of the administration of 3 mg./day DCA, whereas 1 mg./day DCA had caused retention before the circulatory improvement. These authors also report findings [*16*] on non-adrenalectomized dogs with similarly induced heart failure. Only five of seven showed any reduction in GFR, but RBF fell in every case, the average reduction being 31 per cent, resulting in an equivalent rise in filtration fraction.

It is evident from this discussion that the salt retention of congestive heart failure is almost invariably associated with changes in renal filtration fraction. This intimate relationship has been noted and speculated upon by several investigators, including Barger [*37*] who stated that "a rise in filtration fraction implies an abnormally high colloid osmotic pressure in the first portion of the peritubular capillaries. Whether such a force may tend to accelerate the tubular transport of the filtrate is not known." However, if the reabsorption of sodium and water in the proximal tubule is passive and dependent upon the COP in the peritubular capillaries, then the role of filtration fraction as the primary and essential factor in the renal salt retention of cardiac failure becomes clear.

SEQUENCE OF PHYSIOLOGICAL MECHANISMS LEADING TO FLUID RETENTION AND CONGESTIVE FAILURE

Whenever the cardiac output becomes inadequate to meet the total metabolic requirements of the patient with cardiac disease, RBF is decreased (the mechanisms responsible for this are not understood at the present time). This decrease in RBF, with no or very slight change in GFR, results in an increased filtration fraction, which causes an abnormally large rise in the COP within the peritubular capillaries. This increased COP promotes tubular reabsorption, resulting in the retention of salt and water. This series of events must occur quite frequently and in exaggerated form in patients with a weakened myocardium and reduced cardiac reserve, resulting in a progressive retention of salt and water which the individual is not capable of completely excreting during periods of relative inactivity. There is a gradual expansion of the extracellular volume and a rise in venous pressure. The heart becomes unable to pump the increased venous return, RBF is chronically reduced, resulting in a constantly increased filtration fraction and marked fluid retention. Venous pressure rises higher, resulting in transudation of fluid. It is probably this event [*20,21*], or the decreased effective blood volume [*21*], that stimulates the production of increased amounts of aldosterone. This combination of increased filtration fraction and increased production of aldosterone, as well as the later development of decreased GFR, combine to produce almost complete salt and water retention with the development of the full-blown clinical picture of severe congestive heart failure. The possibility that the mechanisms described in this paper may play an important role in the nephrotic syndrome and cirrhosis also deserves serious consideration.

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Clinical Studies

Observations on the Pathogenesis of Renal Tubular Acidosis*

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RENAL tubular acidosis (RTA), a syndrome that is being recognized and reported with increasing frequency, has as its outstanding characteristic a sustained metabolic acidosis of moderate degree, with depression of serum bicarbonate (HCO_3^-) levels and an approximately equivalent elevation of serum chloride (Cl^-). The genesis of the acidosis lies in a renal tubular dysfunction as a result of which the lower limit of urinary pH appears to be fixed in the vicinity of 6.5 to 7.0 and the titratable acidity (TAC) and ammonium (NH_4^+) content are relatively low.

This disturbance in homeostasis often leads to certain complications which are the usual reasons for recognition of the syndrome. Osteomalacia may develop without gross disturbance in serum calcium or phosphate levels. Renal calculi are frequent and are usually associated with some degree of nephrocalcinosis; the stones contain calcium and phosphate and presumably form because of the combination of hypercalcuria and decreased urine acidity. Isolated episodes of muscle weakness associated with hypokalemia have been described. Many patients have polyuria and limitation of concentrating power. Signs of glomerular insufficiency are minimal or absent.

This syndrome has been described in infants [*1–3*] and in adults [*4–6*]. Recent descriptions of a familial incidence [*7*] suggest that in at least some instances RTA is a congenital disorder, but cases have not been followed up long enough to afford adequate knowledge of the natural history of the syndrome. The disorder may occur as a solitary defect or together with other renal tubular diseases such as glycosuric osteomalacia and the Fanconi syndrome.

The precise abnormality in renal tubular function in RTA is not known. Until the publication of a paper by Latner and Burnard in 1952 [*8*] it was widely assumed that a deficiency in renal tubular carbonic anhydrase activity best accounted for the abnormalities seen in RTA. Latner and Burnard, however, described marked increases in urinary TAC and NH_4^+ content and falls in pH after infusion of massive doses of neutral isotonic phosphate solution in a group of infants with RTA. They concluded that the mechanism for acidification of the urine was intact, but was physiologically inhibited by an excess of HCO_3^- reaching the distal convoluted tubules. They further concluded that HCO_3^- was inadequately reabsorbed in the proximal convoluted tubule and that the presence of an excess of phosphate ion somehow corrected this abnormality. Others have accepted the thesis that all the abnormalities in RTA are secondary to defective tubular HCO_3^- reabsorption [*9,10*].

During the past six years we have had the opportunity to carry out studies on five adult patients with typical RTA. Our findings do not confirm those of Latner and Burnard. They provide evidence against any fundamental defect in HCO_3^- reabsorption and against a depression of tubular carbonic anhydrase activity. They fail to provide an adequate explanation for what appears to be the primary defect in RTA, namely, an inability to lower the pH of the urine appropriately.

MATERIALS AND METHODS

Brief case records of the five patients are appended; a more detailed presentation of the clinical data in three of them appears in a previous publication [*11*]. The control subjects were hospitalized patients con-

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valescing from a variety of diseases, such as myocardial infarction and viral hepatitis. The presence of renal disease was excluded by case history, urinalysis and serum urea determinations.

During all experiments involving oral medications both patient and control subjects ingested a neutral ash diet which was begun twenty-four hours before the first urine collection. One or two twenty-four-hour base line periods preceded each experiment. Urine was collected under oil, without refrigeration, but using thymol and chloroform as a preservative. Blood for analysis was withdrawn in the morning preceding administration of the test substance. The experiments using intravenous medications were performed in patients with RTA who had not received alkali therapy from five to seven days and who were in their usual state of mild metabolic acidosis.

Response to Ammonium Chloride. Uncoated tablets (2.0 mEq./kg.) were given orally for three successive days to four patients with RTA and to fourteen control subjects. The effects upon urine pH, NH_4^+ and TAC were observed together with changes in the serum electrolytes.

Response to Phosphate Loads. Oral acid phosphate: If patients with RTA have no limitation in urinary titratable acid formation, acidosis should not result from orally administered sodium acid phosphate. To test this hypothesis NaH_2PO_4 was given in increasing doses (calculated to provide 1.0, 1.5 and 2.0 mEq./kg. excess acidity*) on three successive days to nineteen control subjects and to two patients with RTA. Because of its taste and tendency to cause diarrhea it was dissolved in sweetened orange juice and given slowly throughout the day accompanied by small doses of paregoric and milk of bismuth. Changes in urine pH, NH_4^+ and phosphate content, and TAC, together with changes in serum electrolyte levels were recorded.

Intravenous neutral phosphate: The experiments of Latner and Burnard were repeated by noting the effect of a neutral phosphate load on urine pH, TAC, NH_4^+ content and on the clearance of electrolytes. Three fasting patients with RTA were given intravenous infusions of neutral isotonic sodium phosphate (10 cc./kg.) over a two-hour period in the morning. Urine was collected by catheter drainage under oil for two thirty-minute control periods and during four thirty-minute periods of phosphate infusion. Inulin was administered at a constant rate during the entire procedure. Blood samples were withdrawn at the mid-point of each thirty-minute period.

Oral neutral phosphate: To demonstrate a possible ameliorative effect of a prolonged neutral phosphate load on the metabolic acidosis of RTA, 12 gm. of a mixture of Na_2HPO_4 and NaH_2PO_4 (pH 7.4) were given daily for four days to one patient (D. H.) with RTA; urinary TAC, NH_4^+ and phosphate content and blood electrolyte values were measured during this period.

Response to Bicarbonate Loading. In order to observe the renal "threshold" for HCO_3^- and the tubular capacity for HCO_3^- reabsorption, three fasting patients with RTA were given intravenous infusions of 7 per cent $NaHCO_3$ solution at a rate of approximately 2 cc./minute for two hours. While the serum HCO_3^- rose, urine pH, TAC and NH_4^+ content were observed, together with the excretion and reabsorption of HCO_3^- and other electrolytes. Two thirty-minute control periods preceded four thirty-minute periods of HCO_3^- infusion. Inulin clearance and blood and urine collections were performed in the same manner as in the intravenous phosphate experiments and approximately the same degree of metabolic acidosis was present in the three patients.

Response to Administration of Acetazolamide. The response to acetazolamide offered a potential means of evaluating renal carbonic anhydrase activity in our patients with RTA. Accordingly, after a twenty-four-hour base line period, acetazolamide was administered orally for twenty-four hours (250 mg. three times a day) to two patients with RTA and to two control subjects of comparable size. The twenty-four-hour urine volume, pH, TAC and NH_4^+ content and the serum electrolyte values were compared before and during acetazolamide administration.

CHEMICAL METHODS

Blood pH was measured with a glass electrode and pH meter at 37°c. in a constant temperature block. Urine pH was measured at room temperature with the pH meter. Urine NH_4^+ was determined by aeration using a modification of the method of Van Slyke and Cullen [*12*]. Urinary TAC was measured by the technic of Henderson and Palmer [*13*]. Serum and urine HCO_3^- were determined by the titration method of Van Slyke [*14*], using the pH meter. Urine and serum Na^+ and K^+ were measured with an internal lithium standard flame photometer, serum Cl^- by the method of Schales and Schales [*15*], urinary Cl^- by the Volhard-Arnold method [*12*], urine and serum phosphate by the method of Simonsen et al. [*16*] and inulin by the technic described by Roe [*17*].

RESULTS

Response to Administration of Ammonium Chloride. The control subjects receiving ammonium chloride responded with the characteristic fall in urine pH, gradual rise in urine NH_4^+ and the development of a moderate degree of systemic acidosis. (Table 1, Fig. 1.) Since the dosage of ammonium chloride was based on body weight,

* Because of the approximately 4:1 ratio of Na_2HPO_4 to NaH_2PO_4 in normal plasma it was assumed that 80 per cent of the administered dose of NaH_2PO_4 acted as "excess" acidity.

TABLE I

EFFECTS OF ADMINISTRATION OF AMMONIUM CHLORIDE IN PATIENTS WITH RENAL TUBULAR ACIDOSIS AS COMPARED TO CONTROL SUBJECTS

Subject and Conditions		24-Hour Urine								Serum				
		No. of Observations	Volume (cc.)	pH	NH_4^+		Titratable acidity		HCO_3^-	No. of Observations	Blood pH	HCO_3^-	Cl^-	Na^+
					mEq.	mEq./kg.	mEq.	mEq./kg.	mEq./kg.			mEq./L.	mEq./L.	mEq./L.
Control† Subjects	Base line	55	1640	6.06	24	.36	18	.28	.12	26	7.37	27	105	138
	S.E.*	..	78	.06	1.3	.02	1.0	.02	.01	..	.01	.5	.5	.5
	NH_4Cl day 1	14	1881	5.45	47	.66	30	.43	.09	11	7.35	23	110	139
	S.E.	..	219	.09	4.9	.07	1.4	.01	.01	..	.02	.8	1.1	.5
	NH_4Cl day 2	11	2082	5.13	58	.80	35	.46	.08	8	7.32	22	113	137
	S.E.	..	179	.06	6.4	.06	1.7	.02	.02	..	.01	.9	1.5	1.0
	NH_4Cl day 3	13	2103	5.07	74	1.00	35	.46	.07	10	7.34	22	112	136
	S.E.	..	206	.07	7.9	.08	2.4	.04	.01	..	.01	.9	.7	1.4
J. D.	Base line	2	2500	6.98	24	.50	7	.15	.25	2	7.40	23	113	140
	NH_4Cl day 1	1	2430	6.61	31	.65	12	.25	.15	1	7.29	18	114	139
	NH_4Cl day 2	1	2800	6.59	40	.83	12	.25	.15	1	7.29	17	118	140
	NH_4Cl day 3	1	2480	6.32	47	.98	18	.38	.10	1	7.28	16	‡	141
D. H.	Base line	2	2000	7.00	19	.27	9	.13	.16	1	....	23	113	.....
	NH_4Cl day 1	1	1490	6.69	21	.30	14	.20	.17	1	....	21	116	.....
	NH_4Cl day 2	1	1850	6.56	31	.44	18	.26	.16	1	....	16	118	.....
	NH_4Cl day 3	1	1510	6.40	40	.57	19	.27	.11	1	....	14	123	.....
H. B.	Base line	3	3590	6.80	25	.31	10	.12	.33	1	7.32	18	110	149
	NH_4Cl day 1	1	4590	6.92	34	.41	8	.10	.45	1	7.27	‡	111	144
	NH_4Cl day 2	1	4950	6.80	50	.61	20	.24	.30	1	7.24	‡	112	.....
	NH_4Cl day 3	1	3795	6.50	41	.50	15	.18	.23	1	[7.27]	‡	115	138
M. T.	Base line	..	....	....	....	....	....	...	...	1	7.38	24	112	.....
	NH_4Cl day 1	..	....	....	....	....	....	...	...	..	....	....	.....	.....
	NH_4Cl day 2	..	....	....	....	....	....	...	...	1	7.12	15	121	.....
	NH_4Cl day 3	..	....	....	....	....	....	...	...	1	7.10	13	122	.....

* S.E. standard error of the mean.

† All values reported for the control subjects are mean values. Base line measurements include from one to three twenty-four-hour urine samples from subjects used as controls for both NH_4Cl and NaH_2PO_4 experiments. Blood specimens were not obtained from all control subjects.

‡ Results not obtained due to technical problems.

NH_4^+ content and TAC have been expressed in Table I both in mEq./twenty-four hours and in mEq./kg./twenty-four hours. The average twenty-four-hour urine NH_4^+ rose from a basal value of 24 mEq. (.36 mEq./kg.) to 74 mEq. (1.0 mEq./kg.) on the third day of ammonium chloride administration. TAC increased moderately from 18 mEq. (.28 mEq./kg.) to 35 mEq. (.48 mEq./kg.). The pH of the twenty-four-hour urine fell from 6.06 to 5.07. Serum HCO_3^- fell from a basal level of 27 to 23 mEq./L. on the first day of ammonium chloride administration and was still depressed (22 mEq./L.) after three days of medication. Serum Cl^- rose from 105 to 112 mEq./L. In none of the subjects did symptoms attributable to the acidosis develop.

By contrast, all our patients with RTA tolerated ammonium chloride poorly. Two (J. D. and M. T.) had previously become ill with nausea, vomiting and weight loss when ammonium chloride had been given in the treatment of urinary tract infection. All four patients who were given ammonium chloride under the test conditions felt ill during the last day of the test period. Systemic acidosis increased in each patient to about the same degree as the average of the control patients, or slightly more, but because acidosis was present in the basal state in the patients with RTA the final serum HCO_3^- levels were lower (16, 14 and 13 mEq./L.). Whole blood pH fell (in M. T. to as low as 7.10) and serum Cl^- increased. (Table I.) Urinary NH_4^+ and TAC rose moderately in the three patients with RTA in whom these modalities were measured. In only one patient (J. D.) was the rise in NH_4^+ within the normal range as defined by the control subjects. The maximal twenty-four-hour NH_4^+ output seen in the patients with RTA was 50 mEq. (H. B. on the second day of ammonium chloride administration) compared with the average value of 74 mEq./twenty-four hours on the third day of

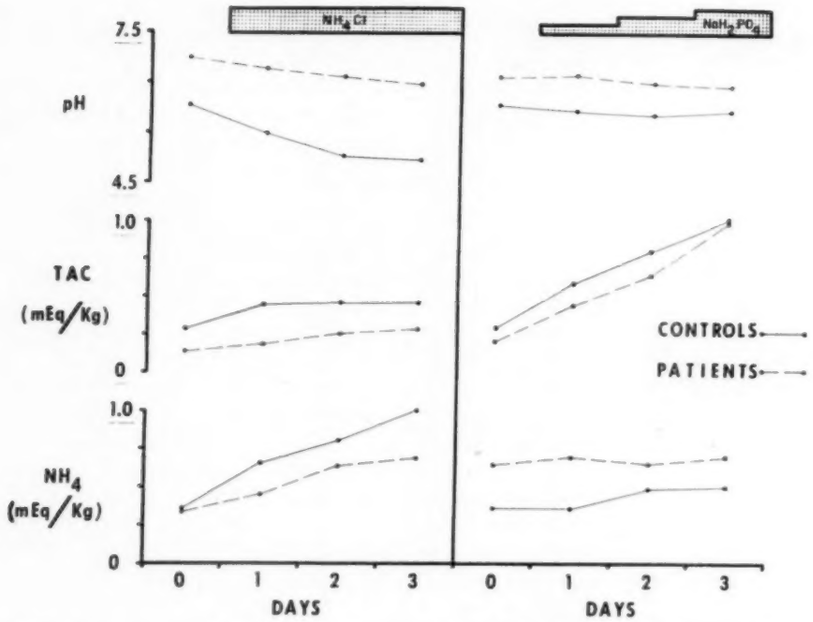

FIG. 1. Comparison of the urinary responses of patients with renal tubular acidosis and control subjects to administration of ammonium chloride and of sodium dihydrogen phosphate.

TABLE II

EFFECTS OF ADMINISTRATION OF SODIUM DIHYDROGEN PHOSPHATE IN PATIENTS WITH RENAL TUBULAR ACIDOSIS AS COMPARED TO CONTROL SUBJECTS

Subject and Conditions		24-Hour Urine						Serum				
		No. of Observations	Volume (cc.)	pH	Phosphate (mM./kg.)	NH_4 (mEq./kg.)	Titratable Acidity (mEq./kg.)	No. of Observations	Blood pH	HCO_3^- (mEq./L.)	Cl^- (mEq./L.)	Na^+ (mEq./L.)
Control* Subjects	Base line	55	1640	6.06	.31	.36	.28	26	7.37	27	105	138
	Phosphate day 1	18	1464	5.93	.60	.36	.58	7	7.37	27	106	138
	Phosphate day 2	18	1576	5.79	.91	.48	.80	8	7.36	28	106	137
	Phosphate day 2	16	1599	5.92	1.34	.50	1.02	9	7.36	27	107	139
J. D.	Base line	2	2325	6.64	.46	.67	.15	1	....	22	114	143
	Phosphate day 1	1	1930	6.51	.93	.63	.44	..	....	..	...	...
	Phosphate day 2	1	2220	6.51	1.45	.65	.58	1	....	22	113	138
	Phosphate day 3	1	2160	6.50	1.88	.67	.88	1	....	20	115	141
D. H.	Base line	1	2220	6.50	.32	.61	.27	1	....	19	116	...
	Phosphate day 1	1	1890	6.69	1.03	.76	.44	..	....	..	...	...
	Phosphate day 2	1	1660	6.50	1.29	.67	.69	..	....	..	...	...
	Phosphate day 3	1	1550	6.37	1.70	.74	1.14	1	....	19	117	...

* All values reported for the controls are mean values. Base line measurements include from one to three twenty-four-hour urine samples on subjects used as controls for both NH_4Cl and NaH_2PO_4 experiments. Blood specimens were not obtained from all control subjects.

ammonium chloride in the control patients. (Table I, Fig. 1.)

The pH of the twenty-four-hour urine fell only minimally in the patients with RTA, the lowest value being 6.32 in patient J. D. on the third day of ammonium chloride administration compared to the mean twenty-four-hour urine pH in the control patients of 5.07. (Table I, Fig. 1.)

Bicarbonate excretion was greater in the patients with RTA than in the control subjects during the ingestion of ammonium chloride. (Table I.)

Response to Phosphate Loads. Oral acid phos-

phate: The effects of the ingestion of NaH_2PO_4 in two patients with RTA and ten control subjects are compared in Table II and Figure 1. There was no progression of acidosis in either group except for a minimal fall of doubtful significance in HCO_3^- in J. D. Urinary excretion of titratable acid and phosphate increased comparably in both patients with RTA and control subjects. Urine pH and NH_4^+ content did not change significantly. Urine NH_4^+ levels in the two patients with RTA were higher than during the base line periods preceding the ingestion of ammonium chloride. Presumably this represents a continued effect of the ammonium chloride experiments that had terminated only three days previously.

Intravenous neutral phosphate: The three patients with RTA in whom this procedure was performed responded uniformly. (Table III.) Serum phosphate levels rose to varying degrees (from four to fourteen times the control value) and the urinary output of phosphate increased correspondingly. There was a marked increase in urinary TAC to levels from eleven to seventeen times the basal output. Urinary NH_4^+ and HCO_3^- output did not change appreciably. Urine pH fell moderately, but to a level no lower than 6.28. Urinary pCO_2 rose significantly in each case. Significant changes were not demonstrated in the other serum and urine electrolytes except for a fall in serum Cl^- and a rise in serum Na^+ in the two patients in whom marked increases in serum phosphate occurred.

Oral neutral phosphate: Acidosis and hyperchloremia were present initially in the single patient (D. H.) with RTA who was given neutral phosphate. Urinary TAC increased immediately and the acidosis and hyperchloremia improved. (Table IV.) After two days of phosphate ingestion serum HCO_3^- had risen from 18.5 to 25.5 and serum Cl^- had fallen from 116 to 112 mEq./L. The urine pH then began to rise and TAC to fall although the excretion of phosphate remained the same.

Response to Bicarbonate Loading. Intravenous sodium bicarbonate administration resulted in a rise to high normal serum HCO_3^- levels in all three patients with RTA. Urinary HCO_3^- excretion appeared to increase minimally in the two patients in whom the urinary pH rose but the change is not statistically significant when the results for the three patients are averaged. (Table V, Fig. 2.) Calculation of the amount of HCO_3^- reabsorbed per 100 ml. of glomerular

TABLE III

EFFECTS OF INTRAVENOUS INFUSION OF NEUTRAL ISOTONIC PHOSPHATE SOLUTION IN THREE PATIENTS WITH RENAL TUBULAR ACIDOSIS

Patient	Period After Start of Infusion*	Inulin Clearance (cc./min.)	Serum					Urine								
			P (mM./L.)	HCO_3^- (mEq./L.)	Cl^- (mEq./L.)	K^+ (mEq./L.)	Na^+ (mEq./L.)	P (μM./min.)	HCO_3^- (μEq./min.)	NH_4^+ (μEq./min.)	TAC (μEq./min.)	Na^+ (μEq./min.)	K^+ (μEq./min.)	Cl^- (μEq./min.)	pH	pCO_2 (mm. Hg)
H. V.	0†	56	1.5	19.0	116	3.5	139	15	33	35	15	432	43	477	6.90	24
	1	59	....	....	...	...	...	40	25	35	25	...	...	...	6.74	20
	2	48	2.9	....	116	3.4	139	58	14	24	30	140	32	99	6.75	19
	3	65	3.3	....	...	...	...	116	16	33	63	...	...	...	6.71	24
	4	52	5.9	20.0	117	3.0	139	171	30	29	91	237	32	45	6.53	84
D. H.	0†	69	2.1	19.5	126	4.2	138	15	25	38	19	...	42	197	6.61	23
	1	72	4.9	....	...	...	...	36	45	38	56	...	...	...	6.48	62
	2	72	8.7	....	...	...	...	111	29	39	126	...	...	...	6.34	95
	3	64	9.4	....	...	...	...	248	33	39	130	...	...	...	6.28	191
	4	70	9.2	20.0	120	3.8	143	252	37	35	134	...	61	63	6.31	191
M. T.	0†	40	1.2	18.0	124	4.0	141	16	26	24	12	57	65	89	6.55	61
	1	36	1.9	....	...	...	...	38	..	24	20	...	..	...	6.50	65
	2	40	2.7	....	...	...	...	63	24	26	72	...	..	...	6.39	110
	3	44	5.0	....	...	...	...	178	..	25	108	...	..	...	6.35	139
	4	48	16.7	19.0	98	3.0	161	264	46	29	168	331	93	104	6.35	121

* Approximately thirty-minute periods.
† Mean of two thirty-minute base line periods.

TABLE IV

EFFECT OF INGESTION OF NEUTRAL PHOSPHATE SOLUTION IN RENAL TUBULAR ACIDOSIS (CASE D.H.)

24-Hour Period	24-Hour Urine				Blood pH	Serum *			
	Volume (cc.)	pH	Titratable Acidity (mEq.)	NH_4^+ (mEq.)		HCO_3^- (mEq./L.)	Cl^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)
Base line	1150	†	9	19	7.37	18.5	116	138	3.9
Phosphate 1	950	6.44	33	24	7.35	21.5	114	...	...
Phosphate 2	840	6.48	39	24	7.38	25.5	112	...	...
Phosphate 3	1005	6.74	23	19	7.38	27.0	111	...	...
Phosphate 4	1485	7.00	12	18	....	27.0	109	147	4.5

* Blood samples were taken at the end of each twenty-four-hour period.

† Not obtained due to technical problems.

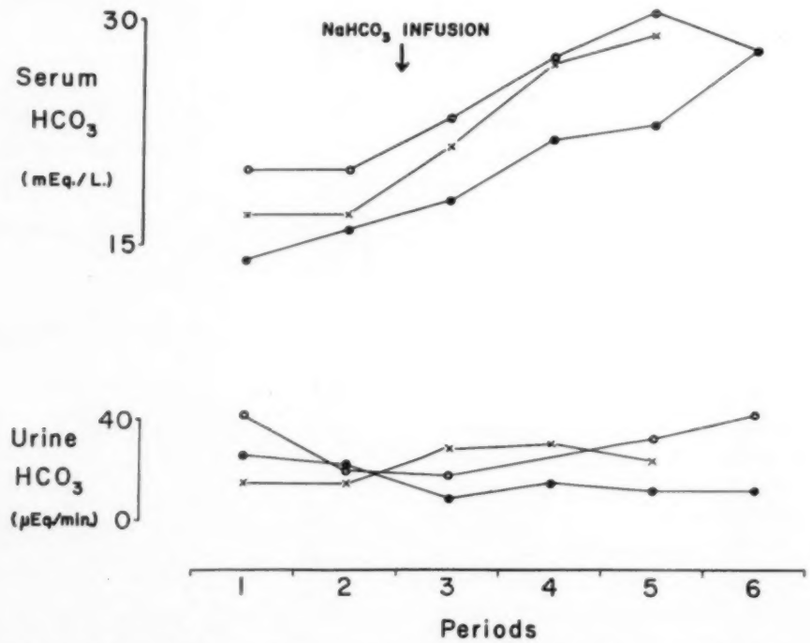

FIG. 2. Failure of urinary bicarbonate to increase following intravenous infusion of 7 per cent sodium bicarbonate in patients with renal tubular acidosis.

filtrate gave values from 2.75 to 3.02 mM./minute when serum HCO_3^- levels were in the high normal range.

Serum Cl^- levels fell from 4 to 10 mEq./L. as the HCO_3^- levels rose. Serum Na^+ levels rose in the two patients in whom they were measured. There were small increases in Na^+ and Cl^- output in two instances and none in the third. Consistent changes were not noted in the other urine and serum electrolytes except for a moderate fall in serum K^+ level.

Response to Administration of Acetazolamide. The two control subjects had the customary response to acetazolamide, namely: an increase in urine volume, a marked rise in urine pH, and an approximately twelvefold increase in HCO_3^- excretion. Serum HCO_3^- fell and Cl^- increased.

The response of the two patients with RTA was qualitatively similar but quantitatively considerably less. The urine volumes increased. The urine pH rose and HCO_3^- excretion increased from 12 to 32 mEq. in patient H. V. and

from 11 to 26 mEq. in patient J. D. There was a slight increase in the degree of acidosis in J. D., no change in H. V. (Table VI.)

Inulin Clearance. Inulin clearance was measured twice in each of three patients with RTA and was found to be reduced. The mean values, corrected to 1.73 m^2 of surface area, were as follows: H. V., 59 cc./minute; D. H., 74; and M. T. 68.

COMMENTS

In the studies reported herein the most obvious difference between patients with RTA and control subjects lies in the inability of the former to maintain homeostasis in the face of a strong acid load. The normal renal response to the administration of a strong acid (i.e., ammonium chloride) is a fall in urine pH and a rise in NH_4^+ output with a minimal increase in TAC, as exemplified by our control subjects. Several days ordinarily are required before the NH_4^+ output increases sufficiently to overcome the initial moderate acidosis that may be produced. This pattern of response is well defined by the work of others and our control subjects were included only in an effort to develop a practical diagnostic test for RTA. The response of our patients with RTA to ammonium chloride administration, although qualitatively similar to that of the control subjects, differed quantitatively in several respects. Urinary NH_4^+ excretion increased to a lesser degree, urinary HCO_3^- excretion continued, and urine pH fell only minimally. Systemic acidosis, initially present, progressed in each instance to a serious degree. Any one of these three abnormalities which characterized the urinary response of the patient with RTA to ammonium chloride administration might be regarded as the cause of the acidosis and therefore the fundamental disturbance in the disease. Each of these abnormalities may then be considered in the light of our experimental data.

First, ammonia production in the distal tubule could be diminished because of a deficiency in a necessary enzyme such as glutaminase. Certainly such a defect should result in a metabolic acidosis and a limited defense against ammonium chloride loading. Present evidence suggests that total renal ammonia production is determined by the activity of enzymes like glutaminase and that diffusion of ammonia into the urine as NH_4^+ is then related to urine pH [*18*]. Although urine NH_4^+ levels in the patients

TABLE V

EFFECTS OF INTRAVENOUS INFUSION OF 7 PER CENT $NaHCO_3$ SOLUTION IN THREE PATIENTS WITH RENAL TUBULAR ACIDOSIS

Patient	Period After Start of Infusion*	Inulin Clearance (cc./min.)	Serum				Urine						Reabsorbed HCO_3^- (mM./100 cc. glomerular filtrate)
			HCO_3^- (mEq./L.)	Cl^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	HCO_3^- (μEq./min.)	Cl^- (μEq./min.)	Na^+ (μEq./min.)	K^+ (μEq./min.)	NH_4^+ (μEq./min.)	Titratable Acidity (μEq./min.)	pH	pCO_2 (mm. Hg)	
H. V.	0†	38	15.0	111	139	3.2	24	56	79	158	42	25	6.70	29	1.45
	1	29	18.0	...	...	...	9	...	...	...	17	15	6.80	20	1.85
	2	50	22.0	111	...	...	15	50	...	...	23	22	6.80	26	2.17
	3	36	23.0	111	...	...	12	35	...	...	16	17	6.80	30	2.26
	4	47	28.0	107	145	2.8	12	28	57	82	20	15	6.80	36	2.77
D. H.	0†	80	20.0	114	136	4.5	31	203	...	82	41	32	6.31	55	1.96
	1	62	23.5	111	...	...	18	258	...	...	31	19	6.33	58	2.32
	2	62	27.5	107	...	...	...	186	...	...	21	13	6.58	33	...
	3	87	30.5	106	...	...	33	340	...	...	37	14	6.85	32	3.02
	4	86	28.0	106	...	3.6	42	274	...	94	36	17	6.85	26	2.75
M. T.	0†	93	17.0	115	139	3.4	15	62	61	52	30	17	6.69	34	1.68
	1	..	21.5	...	...	...	29	...	...	...	34	25	6.90	26	....
	2	..	27.0	...	...	...	31	...	...	...	..	..	6.91	23	...
	3	84	29.0	105	143	2.7	24	136	135	63	24	11	7.02	30	2.88

* Approximately thirty-minute periods.
† Mean of two thirty-minute base line periods.

TABLE VI

THE EFFECT OF ORAL ADMINISTRATION OF ACETAZOLAMIDE IN PATIENTS WITH RENAL TUBULAR ACIDOSIS

Subject	24-Hour Period	24-Hour Urine					Blood pH	Serum *	
		Volume (cc.)	pH	HCO_3^- (μEq.)	Titratable Acidity (μEq.)	NH_4^+ (μEq.)		HCO_3^- (mEq./L.)	Cl^- (mEq./L.)
Control subjects †	Base line	888	6.48	5	10	12	7.37	26.5	109
	Acetazolamide ‡	1688	7.65	70	0	4	7.31	22.5	115
H. V.	Base line	2590	6.75	12	6	20	7.33	16.0	118
	Acetazolamide ‡	3885	6.92	32	8	22	7.30	17.0	117
J. D.	Base line	1810	6.62	11	10	16	7.33	19.0	115
	Acetazolamide ‡	2540	7.12	26	3	14	7.30	17.0	117

* Blood samples taken at the end of each twenty-four-hour period.
† Mean of two normal subjects with body weight equal to H. V. and J. D.
‡ 250 mg. every eight hours.

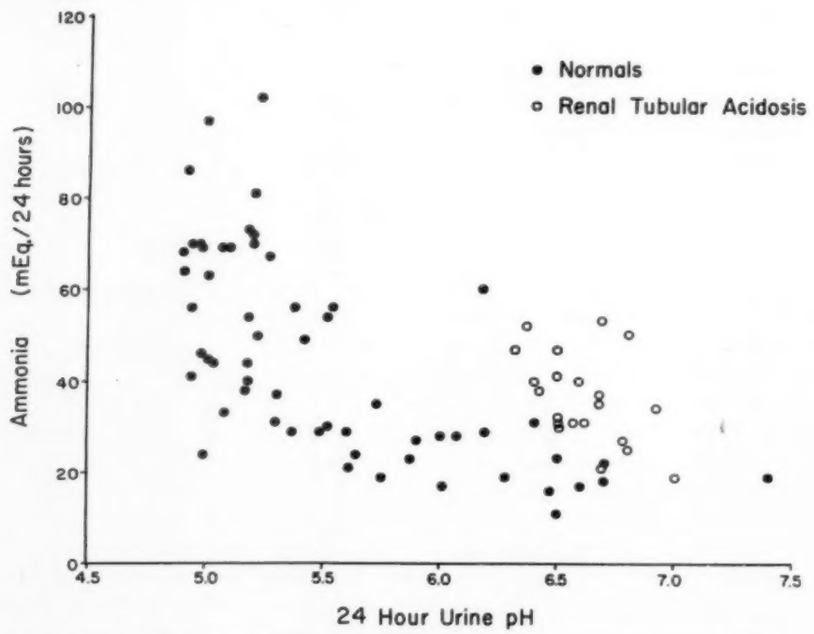

FIG. 3. Comparison of twenty-four-hour urine pH and ammonium content in patients with renal tubular acidosis and in control subjects.

with RTA are low in relation to the degree of systemic acidosis, in relation to urine pH they are actually higher than in the control subjects. Figure 3 plots the relationship between urine pH and NH_4^+ content in the fourteen control subjects and three patients with RTA during and immediately preceding the period of ammonium chloride administration. The NH_4^+ values in the urines from patients with RTA are clearly higher than those in urines of equivalent pH from the control subjects. The finding of a higher than normal urinary NH_4^+ in relation to the urine pH in RTA suggests that NH_4^+ production is normal or above normal in this disease but that it is not appearing in the urine in adequate amounts because of the relatively high pH.

Secondly, defective tubular reabsorption of

HCO_3^-, as postulated by Latner and Burnard [*8*], might be the fundamental physiologic disturbance in RTA. If such a defect exists it ought to become increasingly evident as the serum HCO_3^- rises and the filtered HCO_3^- increases. This did not occur in our patients with RTA who were given $NaHCO_3$ infusions. (Table v, Fig. 2.) Reabsorption of HCO_3^- increased as the serum level of HCO_3^- rose and the filtered HCO_3^- increased. When the serum HCO_3^- reached normal levels, HCO_3^- absorption, when calculated per 100 ml. of glomerular filtrate, was well within the normal limits defined by Pitts and colleagues [*19*]. (The patient with the Fanconi syndrome and RTA described by Milne, Stanbury and Thompson [*9*] also failed to show increased HCO_3^- excretion when the serum HCO_3^- level was raised by oral therapy.) It is true that under all conditions in our patients significant excretion of HCO_3^- in the urine persisted, even when the serum HCO_3^- level was low. This continued excretion of HCO_3^- in the urine is to be anticipated when the urine pH does not fall normally. The current concept of HCO_3^- reabsorption, as expressed by Berliner and Orloff [*20*], postulates that a large proportion if not all of HCO_3^- transfer is effected by the mechanism of tubular hydrogen ion secretion. The pK of carbonic acid is such that the urine pH must drop below the levels seen in our patients with RTA before HCO_3^- can disappear from the urine.

From a quantitative standpoint the third abnormality, failure of the urine pH to fall after administration of ammonium chloride in the patients with RTA, is the most striking one. The lowest twenty-four-hour urine pH observed in the three patients with RTA was 6.32 which is almost four standard deviations higher than the mean third day pH of 5.07 in the control subjects. The highest individual pH among the fourteen control subjects on the third ammonium chloride day was 5.29. Our five patients with RTA all kept records of the pH of their freshly voided urine, determined with nitrazene paper, for prolonged periods (D. H. and J. D. for three months; M. T., H. V. and W. B. each for one month). Readings of 6.0 were very rare and there were none below this level. Nearly all the determinations were 6:5, 7.0 or 7.5.

All the abnormalities noted in the patients with RTA could be explained as a consequence of the failure of the urine pH to fall to normal levels. Urine NH_4^+ levels would then tend to be depressed because of diminished diffusion of ammonia into the tubular urine. Bicarbonate excretion would remain relatively high in the face of systemic acidosis because of the failure of urinary hydrogen ion concentration to rise to normal levels.

However, even if inability to increase the hydrogen ion concentration of the urine is conceded to be the fundamental defect in RTA, this still does not define the nature of the lesion. Unfortunately, of all parameters of urine having to do with acid-base economy we know least about the regulatory mechanisms governing pH. A direct relationship between urinary pH and intracellular pH has been postulated [*20,21*] and is compatible with most clinical abnormalities. Renal tubular intracellular pH must reach very low values to account for urine pH levels as low as 4.5 or 5.0 on the basis of simple diffusion of hydrogen ions from cell to urine. Some as yet unknown mechanism has to be postulated that could allow for attainment of such high hydrogen ion concentrations in the renal tubular cell or for secretion of hydrogen ions into the tubular urine against a significant concentration gradient. A disturbance in this unknown mechanism would appear to be the logical basis for the abnormalities seen in patients with RTA.

Our data indicate that the mechanism that determines the total transfer of hydrogen ions into the urine probably cannot be equated with the mechanism that determines urinary pH. Even though the latter would appear to be functioning inadequately in RTA, there seems to be no unusual limitation in the total number of hydrogen ions that can be transferred into the urine. In the four types of experiments herein described the patients with RTA demonstrated a seemingly normal capacity for total hydrogen ion transfer. After administration of NaH_2PO_4 orally the magnitude of the rise in urinary TAC was about the same in patients with RTA and control subjects. (Table II.) There was no progression of systemic acidosis in either group. Increases in TAC six- to fourteenfold resulted when neutral phosphate loads were given intravenously to three acidotic patients with RTA. (Table III.) Under similar conditions in normal subjects Pitts and colleagues [*19*] demonstrated rises in TAC excretion from two to three times greater than in our patients. However, the difference in TAC excretion appears to be largely due to impaired phosphate excretion in our patients with RTA, no doubt related to their

demonstrably subnormal inulin clearance values. When the ratio of phosphate excretion (mM./minute) to TAC excretion (mEq./minute) is calculated in Pitts' normal subjects it ranges from 1.25 to 1.45. In our patients with RTA the ratio ranges from 1.6 to 1.9. If we accept the thesis that HCO_3^- resorption is accomplished by tubular hydrogen secretion [*20*] then the increased HCO_3^- reabsorption seen in the patients with RTA during $NaHCO_3$ loading provides further evidence of increased tubular hydrogen transfer. Finally, during the ingestion of oral neutral phosphate in patient D. H. a significant increase in urinary TAC occurred (Table IV), indicating increased tubular hydrogen ion transfer.

Demonstration of the precise abnormality in RTA will probably have to await better understanding of the mechanism for urine acidification. However, since carbonic anhydrase is involved in the process of tubular hydrogen transfer, and since subjects receiving acetazolamide have the same biochemical abnormalities as patients with RTA, it is logical to consider a deficiency of carbonic anhydrase as a possible cause of RTA. In the normal subject after administration of acetazolamide not only does the urine pH rise, but total hydrogen transfer (the sum of urinary TAC and NH_4^+ and reabsorbed HCO_3^-) is markedly reduced. Does the ability to increase total tubular hydrogen ion transfer in the patient with RTA make carbonic anhydrase deficiency an unlikely cause of the syndrome? Taggart [*22*], who has reviewed these data, believes that it does. Our opinion (admittedly with no experimental evidence to sustain it) is that we should not exclude the possibility that carbonic anhydrase deficiency might account for the combination of subnormal urinary free hydrogen ion concentration and normal capacity for total hydrogen ion transfer.

The demonstration of a small HCO_3^- diuresis following administration of acetazolamide in two of our patients with RTA (Table III) is conclusive evidence against complete lack of tubular carbonic anhydrase activity in the disease. Although the effect of acetazolamide was much greater in two control subjects, the data do not allow quantitative comparison of carbonic anhydrase activity because of the presence of acidosis in the patients with RTA and the well known tendency of the action of the drug to be diminished under these circumstances [*23*].

One of the intriguing aspects of RTA is the tendency for the metabolic acidosis to stabilize at a level of moderate severity. The failure of the acidosis to progress must mean either that renal tubular mechanisms somehow become "adequate" in the presence of the acidosis or that the metabolism changes in some manner so as to diminish the production of mineral acids and therefore to require less tubular H^+ transfer. Although we have not attempted to analyze our patients' diets carefully, we have noted that they all eat meat and appear to have an acid-ash intake, so we think it unlikely that they are stabilizing their disease by selection of alkaline-ash foods. The most apparent ameliorative influence on the metabolic acidosis of RTA is dissolution of bone. The phosphate anions thus provided act as vehicles for H^+ excretion which in turn allows HCO_3^- reconstitution. This role of phosphate ion is well illustrated in patient D. H., who was given a neutral phosphate salt orally (mixture of Na_2HPO_4 and NaH_2PO_4, pH 7.4). (Table IV.) The usual state of acidosis was present initially but was rapidly relieved by a sharp increase in titratable acid excretion (9 to 40 mEq./day) without any fall in urine pH. Even though the urine hydrogen ion concentration was not raised the total hydrogen excretion was markedly increased by the provision of extra phosphate ions. The sodium ions thus set free were returned to the body as $NaHCO_3$, and serum HCO_3^- rose and Cl^- fell. With disappearance of the acidosis the need for extra H^+ excretion was gone and the urine pH rose and TAC fell. Although demineralization of bone does not always reach the level of radiologic recognition in RTA, it seems likely that it is a constant feature of the disease and that the bone salt has an important stabilizing influence on the acidosis.

In infants with hyperchloremic acidosis Latner and Burnard [*8*] observed a response to intravenous neutral phosphate loading quite different from that noted in our three adult patients. In all the infants the urine pH fell markedly and both NH_4^+ and TAC increased. The urinary pCO_2 fell. Their logical interpretation of the results was that the phosphate load had corrected an inhibitory influence on H^+ and NH_4^+ production. They suggested that the inhibitory influence was an excessive distal tubular concentration of HCO_3^- resulting from inadequate proximal tubular reabsorption. In our adults a very minor fall in urine pH (no

lower than 6.38) accompanied the phosphate infusions, pCO_2 rose instead of falling, and the NH_4^+ output did not change. In the adult patient studied by Milne, Stanbury and Thompson [*9*] an infusion of 600 cc. of isotonic neutral phosphate failed to cause any rise in NH_4^+ output or any decrease in HCO_3^- excretion. The urinary pCO_2 rose moderately. Urine pH values are not recorded. We cannot account for the marked difference between our results and those of Latner and Burnard in what seems to be essentially similar experiments. The amount of phosphate given in proportion to body weight appears to have been considerably greater in their infants. Although serum phosphate levels rose to a higher level in our adults, the urine phosphate excretion probably did not reach the levels achieved in the infants (this factor is difficult to assess since excretion levels are reported in their paper in terms of a standard surface area, 1.73 m^2). It is possible that the hyperchloremic acidosis syndrome in infants has a different genesis than in adults, thus accounting for the difference in our findings. It is interesting that in our own adult patients and in those described in the literature the disorder persists for years or permanently while in the infants reported by Hartman [*2*] and Stapleton [*3*] complete recovery appears to have occurred at the ages of twelve months and six months, respectively. In any event the marked fall in urine pH due to the intravenous infusion of a phosphate solution of pH 7.4 is most interesting and requires some other mechanism for the control of urine pH than we have postulated in our discussion.

CASE REPORTS

CASE I. D. H., a forty-six year old Caucasian housewife, had no symptoms relative to her disease until 1950 when she noted mild muscular weakness over a four-month period culminating in a fulminant attack of flaccid quadriplegia associated with a serum K^+ level of 1.4 mEq./L. The muscle weakness responded rapidly to oral administration of potassium. Studies indicated a urinary pH that was constant between 6.5 and 6.9 with a low urine NH_4^+ and TAC. Serum HCO_3^- was depressed (*circa* 19 mEq./L.) and Cl^- elevated (*circa* 117 mEq./L.). There was no indication of nephrocalcinosis, no disturbance in renal concentrating power, and no roentgen evidence of bone demineralization. Moderate hypercalcuria was evident on a low calcium diet. The patient has been treated with a sodium and potassium citrate mixture orally since 1950 and the serum electrolytes have been within normal limits while receiving this treatment. There have been no episodes of muscle weakness. Acidosis and hyperchloremia returned within a week on several occasions when treatment was interrupted for tests.

CASE II. M. T., a fifty-one year old Negro woman, has had complaints suggesting urinary tract stones and infection since 1937. She is known to have passed calcium-containing stones on frequent occasions since 1947. At that time bilateral diffuse nephrocalcinosis was noted on x-ray film. Other findings included polyuria, persistent urinary pH around 7.0, and intolerance to ammonium chloride. There was a history of five short-lived episodes of generalized muscular weakness since 1937.

In November 1951, renal tubular acidosis was diagnosed because of the finding of a persistent hyperchloremic acidosis together with a fixed urinary pH (6.5 to 6.9) and a low urinary NH_4^+ and TAC. Roentgenograms revealed questionable but not definite bony demineralization. Therapy with sodium and potassium citrate was begun, with return of the serum HCO_3^- to normal. Therapy has been continuous since November 1951, with frequent short lapses due to the patient's failure to keep clinic appointments regularly. In May 1953, surgery was necessary to remove a calculus from the left ureter. With this exception she has been free of symptoms to date. The original serum and urine abnormalities are still evident when treatment is discontinued. X-ray films have revealed no obvious change in the extent of the nephrocalcinosis.

CASE III. H. V., a twenty-two year old Mexican woman, had no complaints prior to the passage of a stone in 1948. At this time x-ray films revealed extensive bilateral nephrocalcinosis in addition to a calculus lodged in the lower right ureter. Numerous calculi were passed between 1948 and 1953; the patient required hospitalization on two occasions. Serum calcium and phosphorus levels were always normal. In May 1953, at the time of hospitalization for another ureteral calculus, renal tubular acidosis was suspected because of the roentgenographic picture of nephrocalcinosis. The urine pH varied only between the narrow limits of 6.7 to 6.9. The serum HCO_3^- was 17, Cl^- 112 and K^+ 2.8 mEq./L. and the non-protein nitrogen was 25 mg. per cent. The urinary NH_4^+ and TAC were low. Treatment with sodium and potassium citrate was started in 1953 and continued to date except for brief periods during which tests were performed or during which the patient neglected to take the medications. During this five-year period the serum HCO_3^-, Cl^- and K^+ levels have been normal except when medication has been discontinued. There have been two brief episodes of right costovertebral and flank pain but no calculi were found in the urine. Bony demineralization has not been evident on the x-ray films.

CASE IV. J. D. is a thirty-nine year old Caucasian woman in whom bilateral extensive nephrocalcinosis was discovered when she passed the first of many kidney stones in 1954. The cause of the nephrocalcinosis was not initially determined and ammonium chloride was given because of the finding of a urine pH of 7.0. With the administration of ammonium chloride she became weak and anorexic, and lost several pounds in weight; after a short time she stopped taking the medication. She passed many small calculi during the next year. In June 1955, tests indicated a constant urine pH approximating 6.7, persistent hyperchloremic acidosis, mild hypokalemia, and low urinary content of NH_4^+ and titratable acid. Bone demineralization was not evident on x-ray film. Analysis of the calculi showed the presence of calcium and phosphate. Treatment with sodium and potassium citrate was begun in July 1955. The serum biochemical abnormalities returned to normal, general health improved considerably, and there was immediate cessation of stone passage. On two occasions during the past year a shower of small stones has been passed, although the serum HCO_3^- has remained normal. When treatment was discontinued for short periods hyperchloremic acidosis reappeared.

CASE V. H. B., a twenty-eight year old Caucasian man, first had renal colic in 1946. After several subsequent episodes, bilateral nephrocalcinosis was noted on x-ray film in 1949. An extensive investigation at that time revealed a fixed urine pH of 7.0 that was not altered by ammonium chloride ingestion, persistent hypercalcuria and normal serum calcium and phosphate levels. An exploratory operation, which included splitting of the sternum, was performed with a tentative diagnosis of hyperparathyroidism; three normal parathyroid glands were seen but no tumor could be found. He has continued to pass small calculi frequently to date. He has noted progressive polyuria for the past five years and now passes approximately 3 L. of urine daily. Investigation in 1955 revealed persistent mild hyperchloremic acidosis (serum HCO_3^- 22 to 24 and Cl^- 109 to 114 mEq./L.), urine pH fixed between 6.8 and 7.0, low urine NH_4^+ content and TAC, non-protein nitrogen 36 mg./100 cc., and serum calcium and phosphate levels within normal limits. There was extensive bilateral nephrocalcinosis but no definite bony demineralization was evident on x-ray film. He had complained of occasional short episodes of severe muscle weakness in the past and the serum K^+ level ranged from 3.4 to 3.8 mEq./L. on several occasions in 1955. Treatment with alkali was undertaken for a brief period but then discontinued; we have lost contact with this patient.

SUMMARY

The responses of five adult patients with renal tubular acidosis to maneuvers designed to elucidate tubular function are compared to the responses of control subjects. After oral administration of ammonium chloride, a greater degree of acidosis developed in the patients with renal tubular acidosis than in the control subjects, they excreted less NH_4^+ and HCO_3^- in the urine, and had a smaller drop in urine pH.

The failure of HCO_3^- excretion to increase in three of these patients when their serum HCO_3^- levels were raised to normal indicates that diminished tubular HCO_3^- reabsorptive capacity is not the fundamental lesion in the disease.

Urinary NH_4^+ levels in renal tubular acidosis, although low in relation to the degree of systemic acidosis, proved to be higher than in the urines of equivalent pH of control subjects, suggesting that the capacity for tubular NH_4^+ formation is not impaired in renal tubular acidosis.

Inability to lower the pH of the urine appropriately is considered to be the primary disorder in renal tubular acidosis, continued HCO_3^- excretion and subnormal ammonia transfer into the urine being secondary phenomena. In spite of the relatively low urinary concentration of free hydrogen ion in renal tubular acidosis the total combined urinary hydrogen (titratable acidity) could be markedly increased by oral or intravenous phosphate loads.

Orally administered neutral sodium phosphate (pH 7.4) corrected metabolic acidosis in one patient with renal tubular acidosis by increasing urinary titratable acidity without lowering pH.

An adequate explanation for the inability of the patient with renal tubular acidosis to acidify the urine was not provided. Carbonic anhydrase deficiency seems an unlikely possibility because of the demonstrated ability of the patient with renal tubular acidosis to increase HCO_3^- reabsorbtion and titratable acidity.

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The Mechanism of Proteinuria, and a Study of the Effects of Hormonal Therapy in the Nephrotic Syndrome*

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Few attempts have been made during the past twenty years to study the mechanism of proteinuria by means of clearance technics. In 1936 Bing [*2*] related the amount of protein excreted to the clearance of creatinine. Assuming

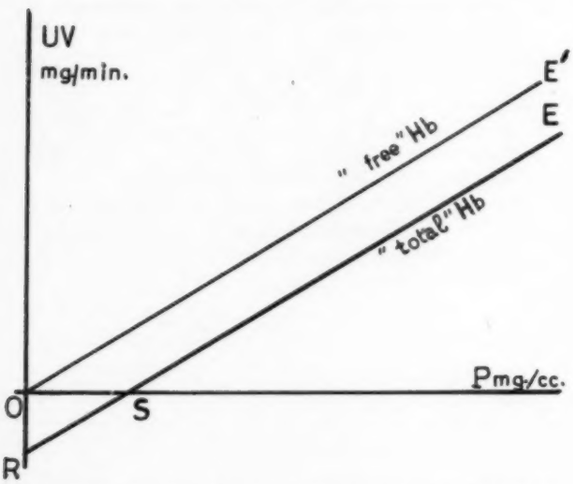

Fig. 1. Relationship between the amount of hemoglobin (Hb) excreted and the plasma levels of "total" and "free" Hb in the dog.

no reabsorption of protein in the tubules he suggested that the ratio

$$\frac{\text{protein excreted mg./minute}}{\text{creatinine clearance}}$$

be used as a measure of the protein concentration in the glomerular fluid. It now seems unlikely that the glomerular filtrate in the normal kidney is completely free of protein [*34*]; and if the protein concentration in the glomerular fluid of normal man is 25 mg. per cent one must assume a daily tubular reabsorption of about 40 gm.

Bing's ratio would not appear to provide an accurate measurement of the protein concentration in the glomerular filtrate of patients with proteinuria since it has not been demonstrated that tubular reabsorption of protein is abolished in these patients. Nevertheless, in 1955 Chinard et al. [*4*] applied this formula to estimate the amount of protein present in the glomerular filtrate of patients with glomerulonephritis. They found it much higher than the 25 to 30 mg. per cent considered normal at normal plasma protein levels. Therefore they concluded that proteinuria could be easily explained on the basis of glomerular hyperpermeability and that a tubular contribution to proteinuria need not be postulated. Chinard et al. did not attempt to interpret their data in terms of glomerular clearance and tubular reabsorption, as had Monke and Yuile in their studies on hemoglobin [*23*]. The latter authors have shown that, above the threshold for hemoglobin (previously measured by Lichty, Havill and Whipple [*15*]), there is a linear relationship between the plasma concentration and the rate of urinary excretion of hemoglobin. From this relationship they calculated three characteristic values of hemoglobin excretion (Fig. 1): (1) The glomerular clearance of hemoglobin (Gl.cl.Hb) which is the volume of plasma cleared of its hemoglobin per minute, and is shown by the slope of the line SE. (2) The threshold below which no hemoglobin is excreted (distance OS). (3) The maximum amount of hemoglobin which the tubules are able to reabsorb (OR), which is equal to OS × Gl.cl.Hb.

Vanderveiken et al. [*33*] have shown recently that the threshold for hemoglobin depends entirely on the linkage of hemoglobin in the plasma

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to an alpha$_2$-globulin (Jayle's haptoglobin [*10*]), the complex being non-filtrable. The relationship between UV_{Hb} and the plasma level of "free" hemoglobin is a straight line passing through the origin (OE′ in Figure 1). Its slope is not different from that obtained by relating UV_{Hb} to the plasma level of "total" hemoglobin.

Although morphological evidence suggests tubular reabsorption of hemoglobin [*11,24*] it appears that this process is quantitatively not sufficient to be measurable in the course of physiological experiments.

A similar relationship has been shown in dogs with three other proteins of different molecular weights (m.w.): myoglobin (m.w. 17,500, Yuile and Clark [*36*]); ovalbumin (m.w. 35,000, Marshall and Deutsch [*21*]) and serum albumin (m.w. 70,000, Malmendier and Lambert [*19*]).

The glomerular clearances of the four proteins studied so far, calculated from the slopes of their $\frac{\Delta UV}{\Delta P}$ relationships, are in good agreement with the concept of molecular sieving through the walls of the glomeruli assuming a cylindrical configuration of the pores with a mean radius of about 35 Å [*12,13,26,27,29*].

From these data it is possible to calculate the concentration of the protein under study in the glomerular fluid as follows:

$$\frac{\text{Glomerular clearance of the protein studied}}{\text{Glomerular filtration rate}} = \frac{C_2}{C_1}$$

where C_2 is the concentration of that protein in the glomerular fluid and C_1 its plasma level. This ratio, the "sieving coefficient," may be used as an index of glomerular permeability to that protein. The value of this coefficient for albumin is 0.006 in normal dogs. Assuming a normal plasma concentration of 4,000 mg. per cent the concentration of albumin in the glomerular fluid should be $4{,}000 \times 0.006 = 24$ mg. per cent, which is in close agreement with the experimental data of Walker et al. [*34*].

In normal man, the authors have succeeded in measuring the threshold for albumin by infusing large amounts of this protein in an acute experiment. Its value is between 7.0 and 7.3 gm. per 100 cc. [*20*]. However they were unable to increase the plasma concentration of albumin high enough to investigate the $\frac{\Delta UV_A}{\Delta P_A}$ relationship. On the basis of similar experiments on dogs there is presumptive evidence that glomerular albumin clearance in normal man does not exceed 0.75 cc./minute. The Tm_A of kidneys in normal man therefore is not greater than 55 mg./minute.

$$Tm_A = \text{Threshold} \times \text{glomerular clearance of albumin}$$
$$= 73 \text{ mg./cc.} \times 0.75 \text{ cc./minute}$$
$$= 55 \text{ mg./minute.}$$

These figures will be used in the first part of this paper for comparison with the data obtained in patients with renal disease.

Loading studies with albumin are easily carried out in patients with albuminuria. However, it was thought necessary to inject large amounts of pure albumin (100 to 150 gm.) in order to investigate the $\frac{\Delta UV_A}{\Delta P_A}$ relationship within a wide range of plasma albumin levels. Previous workers [*4,8*] have generally neglected to do so. However, in the pathological kidney functional homogeneity of the nephrons is unlikely [*25*]. If, as seems probable, different nephrons become albuminuric at different plasma concentrations, the $\frac{\Delta UV_A}{\Delta P_A}$ relationship for albumin will no longer be linear. Therefore the need for investigation over a wide range of plasma albumin levels is obvious.

Competition between proteins for tubular reabsorption, such as has been shown for amino acids [*28*], is another factor which could distort the $\frac{\Delta UV_A}{\Delta P_A}$ relationship from linearity. Hardwicke and Squire [*8*] have suggested that the tubules reabsorb a maximal amount of total protein (Tm_{Pr}) without selection but in proportion to the relative concentrations of the various proteins present in the glomerular filtrate. This would decrease the slope of the $\frac{\Delta UV_A}{\Delta P_A}$ relationship at increasing plasma levels. The role of this factor as well as of the heterogeneity of the nephron population should be considered.

The effects of hormonal therapy (ACTH or prednisone) on proteinuria are reported in the second part of this study, to differentiate tubular effects from changes in glomerular permeability by means of the loading technic here described.

TABLE I

URINARY EXCRETION RATES OF INULIN, PAH, SERUM TOTAL PROTEINS AND SERUM ALBUMIN IN A TYPICAL EXPERIMENT (CASE 6)

Periods	Inulin Clearance* (cc./min.)	PAH Clearance (cc./min.)	Filtration Fraction (%)	Plasma Total Proteins at Tm − 4 (mg./cc.)	Plasma Albumin at Tm − 4 (mg./cc.)	UV Total Proteins (mg./min.)	UV Albumin (mg./min.)	UV Albumin Corrected† (mg./min.)
1	54.7	243	22.5	51.6	17.2	13.9	9.2	9.1
2	62.4	243	25.6	51.6	18.9	16.5	10.7	9.3
3	56.6	220	25.7	51.6	20.5	17.3	12.0	11.5
4	56.6	239	23.6	52.3	22.7	19.7	14.2	13.6
5	52.9	282	18.7	53.6	25.3	23.7	17.8	18.2
6	47.8	305	15.6	55.0	28.1	23.6	18.4	20.9
7	53.2	354	15.0	56.0	30.0	28.5	24.6	25.0
8	51.0	338	15.0	57.1	32.0	34.0	30.0	31.9
9	60.8	421	14.4	58.0	33.7	37.8	32.8	28.3
10	59.4	451	13.1	59.3	35.8	45.1	39.6	36.1
11	50.9	433	14.0	60.9	38.3	44.6	39.3	41.9
12	44.7	380	11.7	62.6	40.9	40.0	36.4	44.2

* Mean 54.2

† Corrected amount of albumin excreted $= \frac{\text{uncorrected amount of albumin excreted}}{\text{inulin clearance of the period}} \times$ mean inulin clearance.

MATERIAL AND METHODS

The procedure was carried out fifty times in eighteen patients, divided into three groups: four patients with amyloidosis, ten with the nephrotic syndrome, and four with chronic glomerulonephritis and marked nitrogen retention. The clinical data for the three groups of patients are summarized in the appendix.

At the beginning of the test an indwelling urethral catheter was inserted into the bladder to allow accurately timed collections of urine every ten to fifteen minutes. The bladder was rinsed with saline solution. A priming dose of inulin and para-aminohippurate was administered and appropriate blood levels were maintained by intravenous infusion at a constant rate. Venous blood was drawn every twenty to thirty minutes, avoiding venous stasis. After an equilibration period of thirty to forty minutes, a first urine collection was made in order to determine the basal glomerular filtration rate, renal plasma flow and protein excretion. Intravenous infusion of serum albumin was then instituted (the Poviet albumin employed is 95 per cent pure on analysis by paper electrophoresis), 50 to 150 gm. being administered at an increasing rate to obtain a rising concentration of serum albumin; ten to fifteen collections of urine were made during the infusion. Then 30 mg. of Evans blue was injected to determine the time necessary for the dye—linked to the albumin—to appear in the bladder urine. This was between six and ten minutes.

Inulin was estimated by the method described by Roe, Epstein and Goldstein [*30*]. PAH was estimated according to Smith et al. [*31*]. Total serum and urinary proteins were estimated by the biuret method as modified by Gornall, Bardawill and David [*5*]. Urinary proteins were precipitated by 10 per cent trichloracetic acid and the precipitate redissolved in 3 per cent NaOH. Electrophoretic analysis of urine and serum was carried out on paper by Grassmann and Hannig's method [*7*], using Schleicher and Schüll filter paper 2043ª. The urine was put in a tight, thin cellophane tubing and exposed to a draught of air at room temperature for two hours. Thereafter it was dialysed first against saline solution and then against veronal buffer; 10 cu. mm. of serum and 20 to 60 cu. mm. of urine were put on the paperstrip in order to obtain an approximately equal amount of protein in each. They were submitted to electrophoresis in the Electrorheophor apparatus for fourteen hours, the current being maintained at 1 amp. per strip. Veronal buffer of ionic strength 0.1 and at pH 8.6 was used. After staining with Amidoschwartz 10B, the strips of paper were cut into the different fractions and eluted in 0.2 N NaOH. The readings were made at 540 millimicrons, using a Zeiss spectrophotometer. Each sample of urine and of serum was analyzed in duplicate.

The results of an illustrative experiment are compiled in Table I. The glomerular filtration rate did not change although the effective renal plasma flow showed a striking increase. These are the usual hemodynamic changes induced in the kidneys by the infusion of albumin. The mean increase in renal plasma flow of ten unselected experiments has been

TABLE II

RESULTS OF LOADING STUDIES PERFORMED IN THE FOUR PATIENTS WITH AMYLOIDOSIS

Case No.	Date	Plasma Albumin (mg./cc.)	GFR (cc./min.)	Glomerular Clearance Albumin (cc./min.)	Threshold for Albumin (mg./cc.)	T_A (mg./min.)	Sieving Coefficient (× 100)	Treatment
1	10/31/55	13.2 to 28.0	102	0.64	6.66	4.26	0.62	None
	1/17/56	11.9 to 29.1	129	0.80	6.55	5.24	0.62	None
	3/27/56	12.0 to 28.0	105	0.97	6.80	6.60	0.92	Prednisone 10 days
	5/ 9/56	10.0 to 24.8	115	1.10	6.40	7.04	0.95	None
	5/15/56	14.3 to 28.2	116	0.97	5.06	4.91	0.84	None
	5/25/56	10.3 to 19.8	126	1.03	5.63	5.80	0.81	None
		19.8 to 33.9		1.48	19.80	(14.70)		
2	3/20/56	10.4 to 21.7	144	0.82	3.78	3.11	0.57	None
	4/20/56	18.7 to 29.4	122	0.75	11.80	8.82	0.61	Prednisone 10 days
	5/11/56	11.4 to 22.2	144	0.81	5.35	4.34	0.56	Prednisone 32 days
3	6/ 5 56	7.5 to 28.9	39.3	0.89	4.92	4.38	2.26	None
4	11/26/56	8.9 to 25.2	96.4	1.41	0.9	1.26	1.46	None
		25.2 to 31.0		4.02	25.2	(67.30)		
	12/10/56	12.7 to 41.9	87.9	0.88	6.7	5.9	1.00	ACTH 10 days

calculated to be 42 per cent of the control level (470 to 670 cc./minute).

The amounts of albumin excreted per minute have been corrected for errors in the collection of urine as follows:

$$\text{Corrected amount of albumin excreted} = \text{uncorrected amount} \times \frac{\text{mean GFR}}{\text{inulin clearance of the period}}$$

The plasma levels of albumin at the mid-point of each period were corrected for delayed excretion of albumin according to the time necessary for Evans blue—which is linked to the albumin—to appear in the urine.

RESULTS

Albumin Loading Tests before Hormonal Therapy

Patients with Amyloidosis (*Four Cases, Table II*). Three of these patients had "pure" amyloidosis with a normal GFR (115, 144 and 96.4 cc./minute). One had a decreased GFR (39.3 cc./minute) as a result of combined amyloidosis and glomerular sclerosis.

Table II shows the results of five loading studies performed on the first patient between October, 1955 and May, 1956. It is obvious that the results were quite reproducible. A straight line relationship between UV_A and P_A is observed in the four experiments in which the plasma level of albumin did not exceed 2.9 gm./100 cc. The threshold was very low (0.66, 0.65, 0.64, 0.50 gm./100 cc.) as compared to a normal value of about 7.0 gm./100 cc. The amount of albumin reabsorbed (T_A)* also was very low (4.26, 5.24, 7.1 and 4.9 mg./minute) assuming a normal value for Tm_A approximating 55 mg./minute. In this patient the slope of the curve increased slightly as the disease progressed (glomerular clearance of albumin = 0.64, 0.8, 0.97, 1.10 and 0.97 cc./minute).

On May 25, 1956, the patient was given an infusion of 125 gm. albumin. The highest plasma concentration reached was 3.5 gm./100 cc. The relationship between plasma levels and UV_A was no longer linear. (Fig. 2.) A break appeared in the slope as the plasma concentration reached 2.0 gm./100 cc. The slope of the second portion of the curve was somewhat steeper than that of the first, but remained linear.

If the change in the slope resulted from the contribution of nephrons, which were not yet

* We shall avoid the term 'TmA' in these cases as the plasma levels reached in these experiments were not high enough to insure saturation of the reabsorptive capacity of all the nephrons. It is clear that in patients with amyloidosis the disease is unequally distributed among the nephrons; therefore some of them may well be unsaturated at a plasma albumin concentration of 2.5 gm./100 cc.

albuminuric at plasma levels lower than 2.0 gm./100 cc., a total glomerular clearance of 1.48 cc./minute and a total T_A of 14.7 mg./minute would result. However it is not certain that this interpretation is correct. Therefore discussion of this point will be reserved until the experimental data are fully presented.

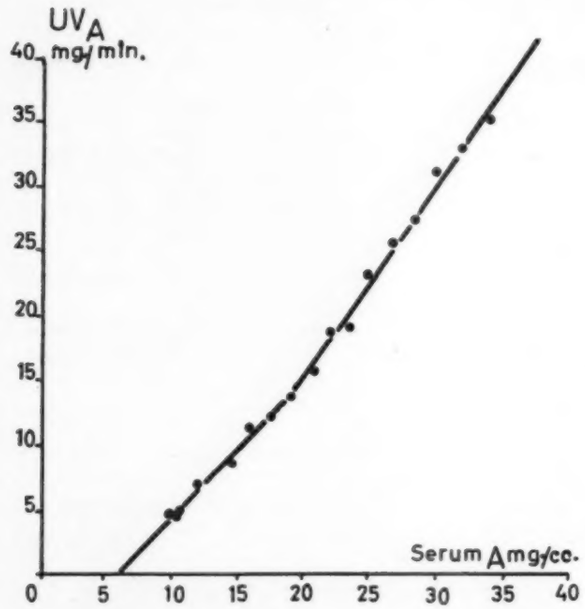

FIG. 2. $\frac{\Delta UV_A}{\Delta P_A}$ relationship in the first patient with amyloidosis. Note the break in the curve at a plasma albumin level of 1.98 gm. per cent.

The results obtained in the second patient who had primary amyloidosis with renal involvement were quite similar. A linear relationship was observed between UV_A and P_A; the glomerular clearance of albumin was 0.82 cc./minute, the renal threshold 3.78 mg./cc.; and the T_A 3.11 mg./minute. The sieving coefficient was 0.57 per cent.

Our third patient, with secondary amyloidosis, had a decreased GFR, 39.3 cc./minute. Despite this, the results of the loading study were comparable to those obtained in the first and second cases (glomerular clearance of albumin 0.89 cc./minute, threshold 4.92 mg./cc., T_A 4.38 mg./minute; sieving coefficient 2.26 per cent).

In the fourth patient, a twenty-nine year old man with primary amyloidosis and a nephrotic syndrome (*cf.* Lindsay's cases [*16*]), a break appeared in the $\frac{\Delta UV_A}{\Delta P_A}$ curve at a plasma level of 2.5 gm./100 cc. The values for the slope, T_A and threshold calculated from the first segment of the curve were comparable to those observed in the three other cases: glomerular clearance of albumin = 1.41 cc./minute; threshold = 0.90 mg./cc.; T_A = 1.26 mg./minute. However,

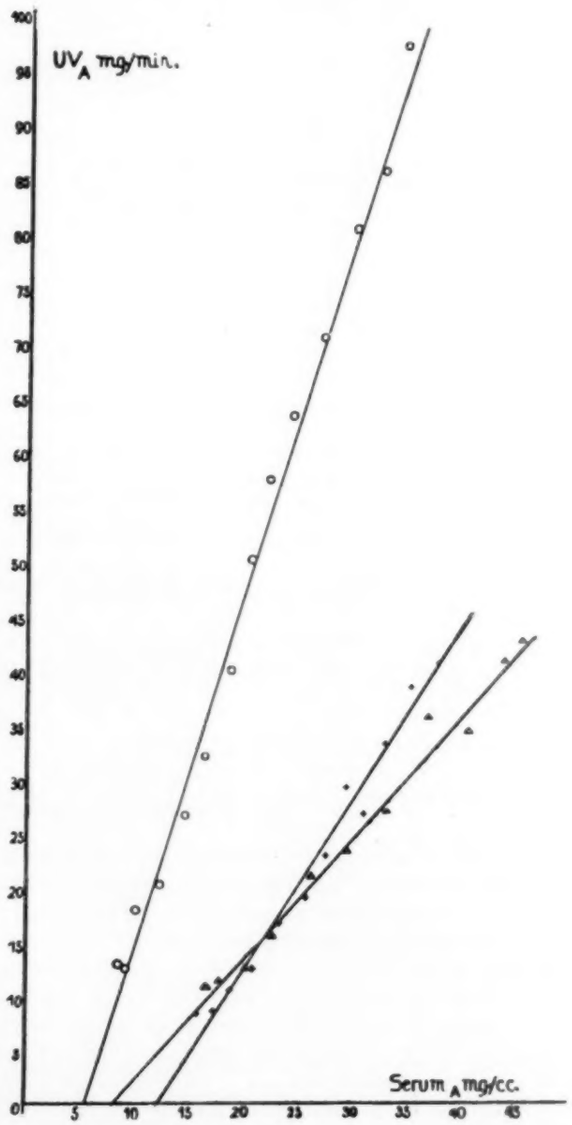

FIG. 3. $\frac{\Delta UV_A}{\Delta P_A}$ relationship in the patients with the nephrotic syndrome belonging to group A: Case 5 (dots), Case 6 (crosses) and Case 7 (triangles).

the slope of the second portion of the curve was much steeper (glomerular clearance of albumin = 4.02 cc./minute) resulting in a total T_A of 67.3 mg./minute if one assumes that the break results from the contribution to albuminuria of a new category of nephrons.

TABLE III

RESULTS OF LOADING STUDIES PERFORMED IN THE TEN PATIENTS WITH A NEPHROTIC SYNDROME*

Case No.	Date	Plasma Albumin (mg./cc.)	GFR (cc./min.)	Glomerular Clearance Albumin (cc./min.)	Threshold for Albumin (mg./cc.)	T_A (mg./min.)	Sieving Coefficient (× 100)	Treatment
				Group A				
5	10/ 1/56	8.7 to 34.1	84.3	3.32	5.7	18.9	3.93	None
	10/16/56	26.3 to 52.9	110		No proteinuria			ACTH 10 days
6	1/22/57	15.8 to 37.5	54.2	1.60	12.3	19.8	2.95	None
	2/1/57	23.6 to 47.	59.6	0.52	12.5	6.53	0.90	Prednisone 10 days
	3/26/57	55.1 to 72.4	87.8		No proteinuria			Prednisone 4 days weekly, 7 weeks
7	2/20/57	16.7 to 45.3	47.8	1.13	8.3	9.4	2.36	None
	3/5/57	18.0 to 41.9	49.5	0.92	12.6	11.6	1.86	Prednisone 10 days
				Group B				
8	3/7/56	22.0 to 31.3	106	0.99	15.2	14.0	0.86	None
		31.3 to 41.4		1.44	31.3	(30.4)	(1.35)	
9	6/21/56	21.3 to 28.1	36.8	1.26	15.5	19.6	3.42	None
		28.1 to 40.6		2.22	28.1	(46.6)	(6.03)	
		40.6 to 46.9		4.71	40.6	(148)	(12.7)	
10	3/22/56	22.9 to 29.6	60.8	0.63	7.1	4.5	1.03	None
		29.6 to 34.1		3.80	29.6	(98.5)	(6.25)	
	4/11/56	30.7 to 41.7	64.4	1.20	26.0	31.2	1.86	Prednisone 10 days
11	5/31/56	32.8 to 43.9	74.2	0.66	28.3	18.7	0.89	None
		43.9 to 55.9		3.69	43.9	(147)	(4.97)	
12	6/25/56	26.8 to 33.1	64.0	0.64	20.6	13.2	1.00	None
		33.1 to 39.4		1.54	33.1	(43.1)	(2.40)	
13	9/25/56	13.6 to 35.6	83.3	0.96	10.1	9.66	1.15	None
		35.6 to 38.9		5.19	35.6	(161)	(6.23)	
	10/8/56	11.9 to 21.1	82.5	1.12	6.67	7.48	1.35	ACTH 10 days
		21.1 to 35.8		2.09	20.4	(27.4)	2.53	
	1/24/57	26.8 to 37.0	83.5	0.96	21.3	20.5	1.14	None
		37.0 to 42.9		3.46	37.0	(113)	(4.14)	
	2/4/57	22.4 to 35.2	72.7	0.77	17.6	13.6	1.05	Prednisone 10 days
		35.2 to 44.8		1.40	35.0	(35.7)	(1.90)	
14	2/22/57	15.1 to 27.1	63.6	0.93	2.3	2.20	1.46	None
		27.1 to 39.4		2.49	27.1	(44.6)	(3.91)	
	3/8/57	17.3 to 24.6	94.4	0.97	8.7	8.44	1.02	Prednisone 10 days
		24.6 to 38.7		2.44	24.6	(44.7)	(2.58)	
	4/9/57	17.1 to 26.1	82.8	1.29	7.6	9.75	1.55	None
		26.1 to 41.0		2.52	26.1	(40.8)	(3.04)	
	4/23/57	13.6 to 20.9	76.9	0.68	0	0	0.88	ACTH 10 days
		20.9 to 32.8		2.38	19.9	(47.5)	(3.09)	

* Group A: Patients showing a straight linear relationship between UV_A and P_A. Group B: Patients showing a break in the $\frac{UV_A}{P_A}$ curve.

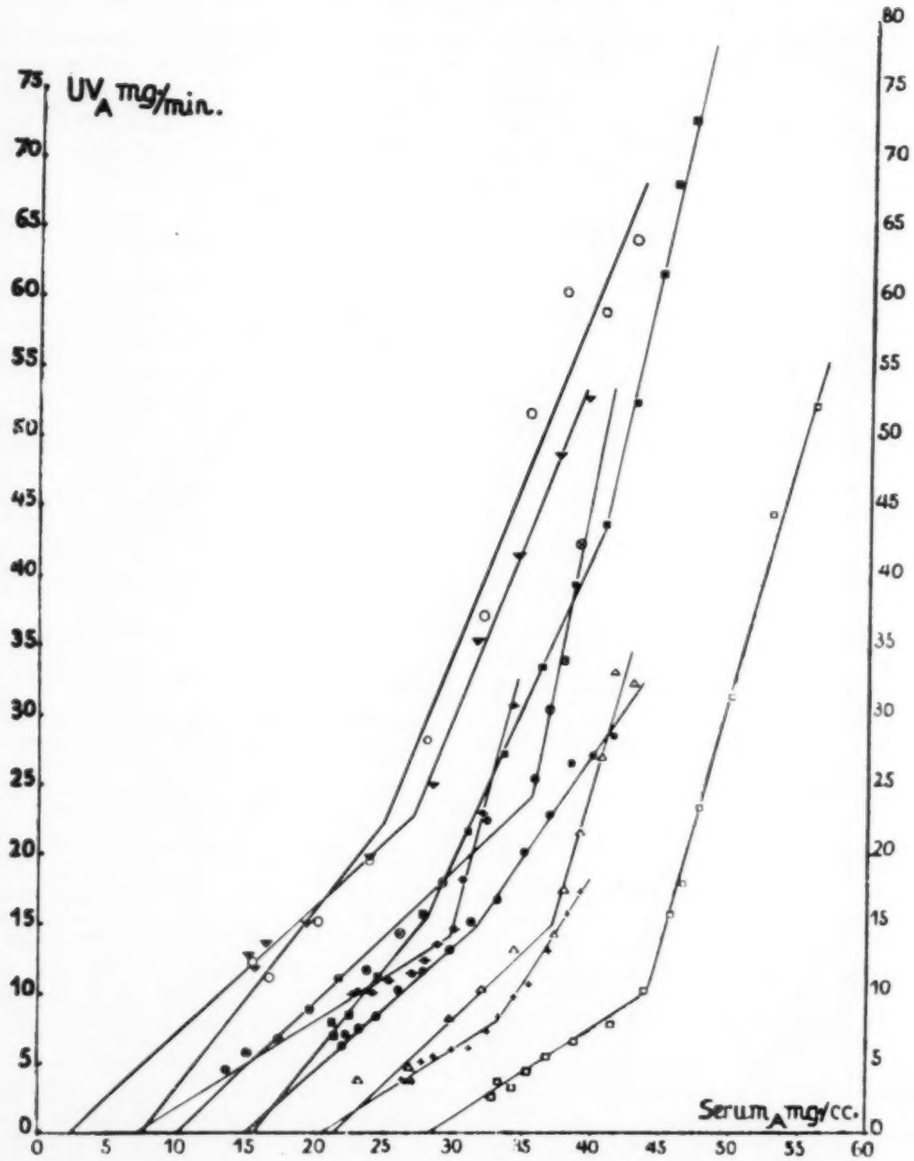

FIG. 4. Results of nine loading tests performed on the patients with a nephrotic syndrome belonging to group B. Note the break in the curve appearing at plasma levels which vary in different patients.

Patients with the Nephrotic Syndrome (*Ten Cases, Table III*). These patients were separated into two groups, not so much on the basis of clinical differences but as a result of the loading tests. Three of these patients (group A) showed a straight linear relationship between UV_A and P_A despite a rapid increase in the blood concentration of albumin to normal levels or even above. Seven patients (group B) showed a break in their $\frac{\Delta UV_A}{\Delta P_A}$ relationship at plasma levels which differed from patient to patient but occurred somewhere between 2.4 and 4.4 gm./100 cc.

Group A. (*Fig. 3*): In the three patients with the nephrotic syndrome who showed a linear $\frac{\Delta UV_A}{\Delta P_A}$ relationship, the glomerular clearance of albumin was 3.32, 1.60 and 1.13 cc./minute. The sieving coefficient was 3.93, 2.95 and 2.36 per cent. The threshold was between 0.6 and 1.3 gm./100 cc. The reabsorptive capacity of the tubules was lower than the 55 mg./minute

TABLE IV

RESULTS OF LOADING STUDIES PERFORMED IN THE FOUR PATIENTS WITH SEVERE RENAL INSUFFICIENCY

Case No.	Date	Plasma Albumin (mg./cc.)	GFR (cc./min.)	Glomerular Clearance Albumin (cc./min.)	Threshold for Albumin (mg./cc.)	T_A (mg./min.)	$\varphi \times 100$
Case 15 — Goo.	2/2/56	28.5 → 39.05	17.5	0.93	16.6	15.32	5.28
Case 16 — Pe.	11/7/55	27 → 35.5	9.5	0.19	1.3	0.25	1.98
Case 17 — Bl.	5/2/56	33.63 → 45.5	11.8	0.26	15.1	3.94	2.20
Case 18 — V.d.P.	12/20/55	41.1 → 46.65	18.8	0.24	19.1	4.58	1.27

taken as a rough estimate of the normal Tm_A (18.9, 19.8 and 9.4 mg./minute). These values may well represent the Tm_A in these cases as plasma levels high enough to saturate all the nephrons were probably reached. Two reasons make this hypothesis most likely: Irrespective of whether hyperpermeability or tubular impairment is responsible for the proteinuria, the threshold for albumin, and hence the plasma level required to saturate the nephrons, must be decreased because of the following relationship:

$$Tm_A = \text{threshold} \times \text{glomerular clearance of albumin}$$

Secondly, because the renal defect responsible for proteinuria is probably more uniformly distributed in the nephron population in the nephrotic syndrome than in amyloidosis.

Group B. (Fig. 4): Group B includes seven patients. Four of them showed the clinical picture of so-called subacute progressive glomerulonephritis (Cases 9, 10, 12 and 14). Their filtration rate was decreased to about 60 per cent of the normal (36.8, 60.8, 64.0 and 63.6 cc./minute at the time of the first loading test). Two patients (Cases 8 and 13) with a normal GFR showed the clinical signs of the nephrotic syndrome without a past history of acute glomerulonephritis. One patient (Case 11) had residual postnephritic albuminuria without symptoms of progressive deterioration of renal function.

Nine experiments were performed. In each case a break appeared in the $\frac{\Delta UV_A}{\Delta P_A}$ curve when large amounts of albumin were infused.

In eight experiments the following pattern was observed: at a plasma level somewhere between 2.4 and 4.4 gm./100 cc. the slope of the curve, which was linear at lower plasma levels, became much steeper although remaining linear within the range of plasma levels investigated. In one case the $\frac{\Delta UV_A}{\Delta P_A}$ relationship seemed rather curvilinear or could be divided into three linear segments with increasing slopes.

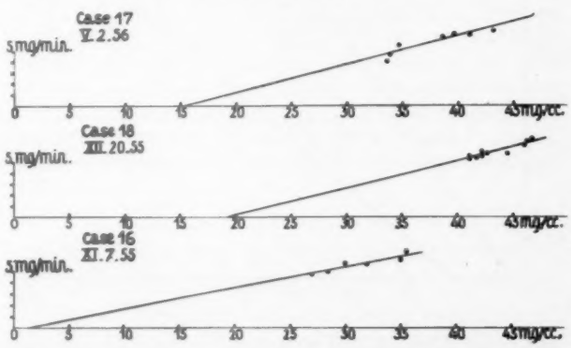

FIG. 5. Results of the loading tests in three patients with severe renal insufficiency (Cases 16, 17 and 18).

If this phenomenon were interpreted in terms of inhomogeneity of the nephron population, the findings would suggest that a category of nephrons with a much higher capacity to reabsorb albumin was saturated at the plasma level at which the break occurred. The amount of albumin reabsorbed per minute would be between 40 and 160 mg./minute (30.4, 40.8, 43.1, 44.6, 98.5, 113.4, 147.9, 148.4 and 161.0 mg./minute) as calculated by extrapolation of the steepest part of the curve. These high figures are most unlikely, therefore another explanation of this phenomenon will be offered (see Discussion).

Patients with Severe Renal Insufficiency (Four Cases, Table IV and Fig. 5). The third group consisted of four patients with renal insufficiency (GFR less than 20 cc./minute). One had

severe proteinuria and plasma protein abnormalities, and closely resembled the cases in group B except for a markedly diminished GFR. The other three had moderate albuminuria and only slight distortion of the plasma protein distribution.

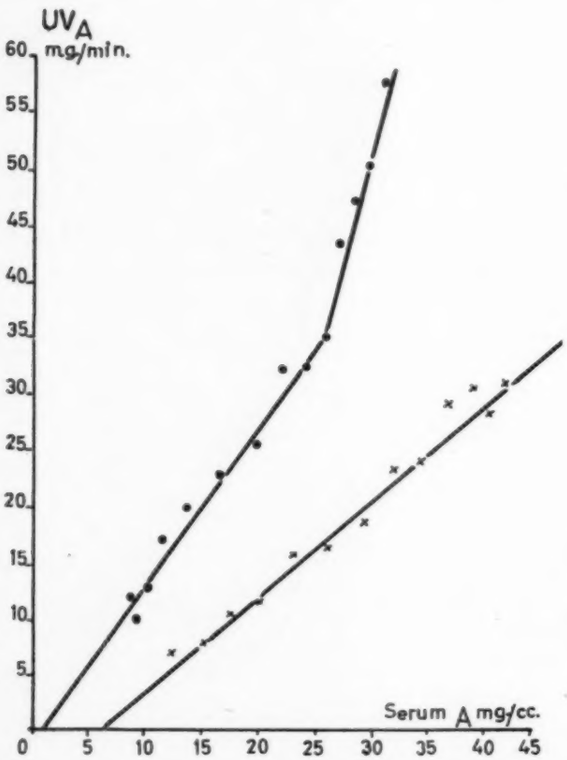

FIG. 6A. Effects of ACTH on the $\frac{\Delta UV_A}{\Delta P_A}$ relationship of a patient with amyloidosis who showed a break in the curve before treatment. Note the decrease in the slope and the disappearance of the break (dots before treatment, crosses after).

The results obtained in the first case were comparable to those observed in the patients with the nephrotic syndrome, and fit well with the clinical picture (glomerular clearance of albumin = 0.95 cc./minute, threshold = 1.66 gm./100 cc., T_A = 15.3 mg./minute; the sieving coefficient is high: 5.28 per cent owing to the low GFR, 17.5 cc./minute).

In the other three cases the $\frac{\Delta UV_A}{\Delta P_A}$ relationship was linear, as shown in Figure 5. The glomerular albumin clearances were very small (0.19, 0.26 and 0.21 cc./minute with sieving coefficients of 1.98; 2.20 and 1.27 per cent). The T_A were very low: 0.25, 3.94 and 4.58 mg./minute. (Table IV.) These results may be readily interpreted if one recognizes that a large number of nephrons are sclerosed and no longer functional.

Effects of Hormonal Treatment on the Excretion of Albumin

The effects of steroid hormones and of ACTH on the clinical course of the nephrotic syndrome have been extensively studied [*1,3,9,14,17,18,22,32*]. These hormones not only induce diuresis in about 60 per cent of the cases treated but also reduce the proteinuria in some of these patients. No attempts have been made to investigate the mechanism of their action on proteinuria. The loading test described in the first part of this paper seemed to provide a favorable means to investigate this problem. The results of nineteen loading studies with albumin (five performed after ACTH administration and fourteen after prednisone administration) will be reported. Only patients belonging to the first two groups (amyloidosis and nephrotic syndrome) have been treated. No attempt was made to treat patients with severe renal insufficiency.

Patients with Amyloidosis (*Table II*). Three of the four patients in this group were given prednisone (40 mg. daily) for ten days. No clinical improvement was observed.

There was no effect on the results of the loading test in the first patient. A slight increase in the threshold and T_A was observed in the second patient, but the slope of the $\frac{\Delta UV_A}{\Delta P_A}$ curve remained unchanged. This result was of short duration and disappeared within twenty days although the administration of prednisone was carried on for thirty-two days. In the fourth patient the administration of prednisone resulted in a decrease of the slope of the $\frac{\Delta UV_A}{\Delta P_A}$ curve. (Fig. 6A.) Even more significant was the fact that the break in the curve which occurred when the plasma level reached 2.52 gm./100 cc. was no longer observed after treatment although a plasma level of 4.19 gm./100 cc. was reached.

Patients with the Nephrotic Syndrome (*Table III*). *Group A:* Two of the three patients in this group (who showed a straight line relationship between UV_A and P_A) responded strikingly to ACTH or prednisone therapy. Protein disappeared from the urine within ten days in Case 5 and loading

with 125 gm. of albumin did not produce albuminuria although it increased the plasma level to 5.2 gm./100 cc. However, this patient relapsed after a few months of freedom from proteinuria. In Case 6, the patient was treated with prednisone for ten days and a sharp de-

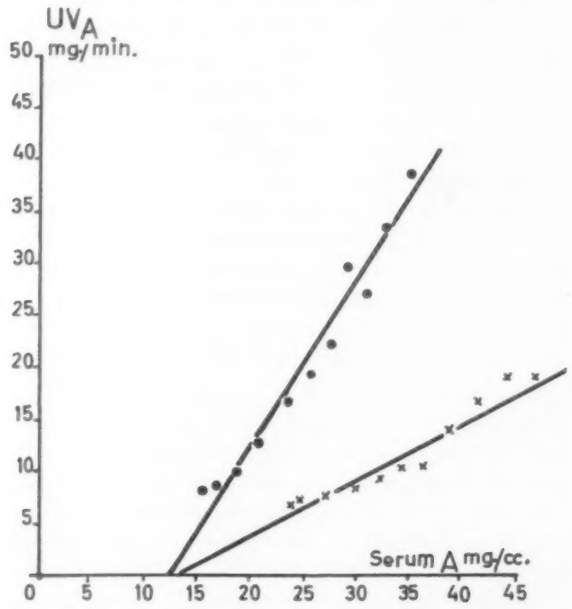

FIG. 6B. Results of the loading studies performed before (dots) and after the administration of prednisone (crosses) in a patient belonging to group II A (nephrotic syndrome). Note the decrease in the slope without change in the threshold.

crease in the slope of the $\frac{\Delta UV_A}{\Delta P_A}$ curve was correlated with significant improvement. The glomerular clearance of albumin decreased from 1.6 to 0.52 cc./minute, the threshold remaining unchanged, and T_A decreased from 19.8 to 6.5 mg./minute. (Fig. 6B and Table III.) Seven weeks later this patient was no longer albuminuric when the plasma level of albumin was increased to 7.24 gm./100 cc., a value which is near the normal threshold for albuminuria; during this period the patient was treated four days a week with prednisone (40 mg. per day). No significant change was observed in the third patient after ten days of treatment with prednisone.

Group B: Within the last two years one of these patients (Case 8) was investigated three times after ACTH and three times after prednisone administration. Five other studies were performed in three other patients of this group. (Table III.)

Case 8. Figure 7 represents the results of the six loading studies in this patient. The broken lines correspond to the control experiments performed before a ten day course of ACTH or prednisone, the solid lines to the experiments performed after treatment.

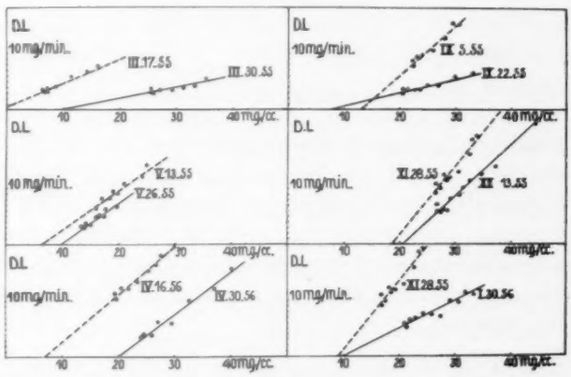

FIG. 7. Results of six loading studies performed after treatment with ACTH on March 30, 1955; May 26, 1956; and April 30, 1956; and with prednisone on September 22, 1955; December 13, 1955; and January 30, 1956, on patient 8 belonging to group II B. Note a significant decrease in the slope on three occasions and an increase in threshold and T_A without change in the slope on two occasions (once very significantly). The interrupted lines show the results obtained in the test performed immediately before treatment, the solid lines those obtained after treatment.

Two treatments, one with ACTH (May 26, 1955) and one with prednisone (December 13, 1955) produced only small changes either in the slope of the curve or in the amount of albumin reabsorbed. On three occasions (March 30, 1955; September 22, 1955 and January 30, 1956) the response was an evident decrease in the slope of the $\frac{\Delta UV_A}{\Delta P_A}$ curve, T_A and the threshold being simultaneously increased in one experiment, unchanged or slightly decreased in the two others. Once (April 30, 1956) this patient responded by significantly increasing the threshold and the amount of albumin reabsorbed, the slope of the curve being unchanged. It was obvious that the best immediate clinical result of treatment was related to the decrease in the slope rather to an increased T_A. However, as a result of the cumulative effects of therapy or of spontaneous healing, the threshold and the T_A progressively increased in this patient, the former from 0 to 2.7 gm./100 cc., the latter from 0 to 20.9 mg./minute [*20*]; the glomerular permeability to albumin did not change significantly. This

result points to the conclusion that, in some patients at least, the tubular defect contributes to the decrease in threshold and to the hypoalbuminemia which are the most characteristic features of the nephrotic syndrome.

Cases 10, 13 and 14. The results of the five loading studies performed on these patients are reported in Table III. In Case 10 a course of prednisone therapy resulted in the disappearance of the break observed in the $\frac{\Delta UV_A}{\Delta P_A}$ curve before treatment although the plasma level of albumin reached in the post-treatment test was much higher than in the pretreatment experiment. The increase in the plasma level of albumin after administration of prednisone was so great that the first part of the curve could no longer be reproduced.

In Case 13 the break in the $\frac{\Delta UV_A}{\Delta P_A}$ curve did not disappear either after ACTH or prednisone administration. The slope of the first part of the curve was not changed. This negative finding fits well with the fact that no clinical improvement was observed. The treatment resulted only in a definite decrease in the slope of the second segment of the curve (from 3.46 cc./minute to 1.4 cc./minute after prednisone administration, and from 5.19 to 2.09 cc./minute after ACTH therapy).

In Case 14 administration of ACTH or prednisone did not modify the characteristic values calculated from the two segments of the $\frac{\Delta UV_A}{\Delta P_A}$ curve, although the glomerular filtration rate increased after the first course of prednisone from 63.6 to 94.4 cc./minute. ACTH seemed to decrease the slope of the first part of the $\frac{\Delta UV_A}{\Delta P_A}$ curve; however, the number of periods on which the calculation of this segment of the $\frac{\Delta UV_A}{\Delta P_A}$ curve is based is too small to permit accurate estimation of the glomerular clearance of albumin at low plasma levels.

COMMENTS

Significance of the Results of the Albumin Loading Tests. From the results of the loading tests with albumin it would appear that the relationship between the amount of albumin excreted and the plasma albumin level may be expressed either by a straight line (irrespective of the degree of increase in the plasma albumin concentration induced) or by two linear segments, the second of increasing slope. The necessity for investigating this relationship within a wide range of plasma levels is therefore apparent. No correlation could be made out between the type of response of the kidney and the nature of the renal disease. Both patterns were observed in amyloidosis and in the nephrotic syndrome with or without subacute progressive glomerulonephritis. However, patients with severe renal insufficiency failed to exhibit a second segment of increasing slope.

The experimental data are readily interpreted when the relationship is linear. In this case two interpretations may be given of these data. If the disease is nearly equally distributed among the nephrons, which is likely in nephrosis, the values for glomerular clearance of albumin, threshold and T_A represent the means of individual glomerular clearances of albumin, t_A and thresholds of the whole population of nephrons. Then the value for the sieving coefficient is correct. On the other hand, if some of the nephrons remain unaltered, which is more likely in amyloidosis, these values only represent the glomerular clearance of albumin, threshold and T_A of those nephrons which are proteinuric at the plasma levels investigated. Then the sieving coefficient is not a correct measure of their permeability to albumin, as the glomerular clearance of albumin of only a proportion is related to the total volume of GFR. This may well explain the apparently normal values for the sieving coefficient (0.62 and 0.57 per cent) observed in two of the patients with amyloidosis. These values were significantly higher in the three patients with the nephrotic syndrome of group A (3.9, 2.9 and 2.3 per cent).

The significance of the break which appeared in the $\frac{\Delta UV_A}{\Delta P_A}$ curve in nine of the eighteen patients studied (two with amyloidosis and seven with the nephrotic syndrome) is not entirely clear. The hypothesis that a category of nephrons which were not albuminuric at lower plasma albumin levels became saturated at this particular value of P_A seems unlikely, because this would imply that in these patients some nephrons were able to reabsorb much larger amounts of albumin than the others, resulting in values for T_A much higher than the 55 mg./minute estimated for Tm_A in the normal subject. Two other possibilities have been considered: That the

injection of large amounts of albumin, by increasing the plasma volume, enlarges the leaks in the glomerular membranes, resulting in increased glomerular permeability; and that the tubular capacity to reabsorb albumin decreases in the course of the experiment, resulting in an increased output of albumin.

It must be emphasized that measurement of the three values characteristic of the excretion of protein is possible only if conditions do not vary during the experimental procedure [*6*]. If the Tm_A decreased or if the glomerular permeability increased in the course of experiment, the amount of albumin excreted would increase more than could be accounted for by the increment in plasma level. A continuous change of one of these factors would result in a steeper slope of the $\frac{\Delta UV_A}{\Delta P_A}$ curve. The extrapolated value of T_A would no longer have any biological significance. Of the two possibilities suggested, the first is the more likely because the increase in the output of albumin at a given plasma level in some patients exceeded the value of the T_A calculated from the first segment of the $\frac{\Delta UV_A}{\Delta P_A}$ curve.

The concept of an increase in glomerular permeability as the plasma volume increases is supported by observations by Wassermann and Mayerson [*35*]. These authors have shown in dogs that the ratio between the level of albumin in the lymph and that in the plasma is increased when the volume of plasma is expanded with dextrans. Dextrans offer a means of investigating the effects of expanding the plasma volume on the glomerular permeability. This problem is now under investigation in our laboratory.

If this hypothesis is correct, only the first portion of the $\frac{\Delta UV_A}{\Delta P_A}$ curve gives a correct estimate of the glomerular clearance of albumin, the threshold and the T_A in patients who do not show a straight line relationship.

The values calculated from the first segment of the $\frac{\Delta UV_A}{\Delta P_A}$ curve in the patients of group B are in agreement with this hypothesis. The sieving coefficient never is lower than 0.6 per cent but varies between 0.86 and 3.42 per cent from patient to patient.

The very low values of glomerular clearance of albumin, with a sieving coefficient higher than 0.6 per cent, observed in the patients of the third group, who exhibited severe renal insufficiency, are easily explained by the reduced number of functional nephrons present.

In no experiment was a decrease in the slope of the $\frac{\Delta UV_A}{\Delta P_A}$ curve observed as the absolute plasma level of albumin and the proportion of albumin in relation to the other plasma proteins increased. Therefore it was not considered necessary to assume competition of proteins for tubular reabsorption, as suggested by Hardwicke and Squire [*8*].

From a comparison of the values obtained in albuminuric patients with those calculated for normal man it is obvious that albuminuria results from increased permeability of the glomerular walls to albumin. However it seems probable that in most cases a tubular factor contributes to the increase in the amount of albumin excreted. This is suggested by the results obtained in patients with the nephrotic syndrome who showed a straight linear $\frac{\Delta UV_A}{\Delta P_A}$ relationship, despite the fact that the plasma level of albumin was increased to very high values (up to 5.5 gm./100 cc.). In these patients the amount of albumin reabsorbed by the tubules was much less than the 55 mg./minute supposed to represent Tm_A in normal man. It seems reasonable to assume that hyperpermeability is the primary factor and that the tubular defect is the consequence of tubular overloading.

Effects of Hormonal Treatment. The clinical response to the administration of ACTH or prednisone has usually been judged by the disappearance or persistence of edema. Our patients with amyloidosis did not receive any clinical benefit from treatment although in one case a slight decrease in the glomerular permeability was observed in the loading test.

Some correlation between the clinical results and the data obtained by the loading studies was sought. Clinical improvement was accompanied in the most favorable cases (two patients) by the disappearance of albuminuria not only at normal plasma levels but even at plasma concentrations of albumin higher than normal. More frequently (five experiments) a good clinical response was correlated with a decrease in the slope of the $\frac{\Delta UV_A}{\Delta P_A}$ curve in spite of the persistence of albuminuria. In the patients who

showed no clinical improvement there was (in four experiments) a decrease in the slope of the second segment of the curve, resulting in a decrease or disappearance of the break observed before treatment; and in four experiments a slight increase in the threshold and in T_A without any change in the slope of the curve. In some instances the data obtained before and after treatment were quite similar (four experiments).

When proteinuria disappears completely even at high plasma albumin levels we are of course unable to draw any direct conclusion as to the causal mechanism of this phenomenon. However, there is no reason to suspect that one mechanism operates to effect complete disappearance of proteinuria and another to reduce the proteinuria, as observed in those cases in which a decrease in the slope of the $\frac{\Delta UV_A}{\Delta P_A}$ curve occurred.

Three possible mechanisms may be advanced to explain the effect of hormonal therapy in decreasing the slope of the curve: (1) A decrease in abnormal permeability in all the nephrons contributing to proteinuria. In this case T_A would be unchanged and the threshold would increase in proportion to the decrease in the glomerular clearance of albumin. (2) Complete recovery of normal permeability in some of the nephrons which no longer contributed to the proteinuria despite the high plasma albumin levels induced by loading. If this were the case T_A might appear to decrease, the threshold would be unchanged. (3) An increase of tm_A in some nephrons, so that they would no longer be albuminuric at the plasma levels investigated in the post-treatment study. This hypothesis, however, appears unlikely.

There would appear to be little doubt that the most significant effect of the hormones is to restore glomerular permeability by one of the two first mechanisms mentioned. However, in a few cases a slight increase in T_A and threshold was observed without change in the slope of the curve. This suggests that the hormones are also able to enhance tubular reabsorption of albumin. This effect of the treatment generally did not influence the clinical picture as much as correction of the hyperpermeability.

SUMMARY

An albumin loading test is described which makes it possible to relate the amount of albumin excreted (UV_A) to the plasma concentration (P_A) over a wide range of plasma albumin levels. This procedure was employed to study four patients with amyloidosis, ten with the nephrotic syndrome (with or without progressive subacute glomerulonephritis), and four with severe renal insufficiency.

The $\frac{\Delta UV_A}{\Delta P_A}$ relationship was found to be either linear or expressed by two (in one case three) linear segments, the second of increased slope. Both patterns were observed in patients with amyloidosis and with the nephrotic syndrome. A straight linear relationship was always obtained in patients with marked renal insufficiency.

Four characteristic values were calculated from this relationship: the glomerular clearance of albumin ($Gl.Cl._A$), the threshold for albumin, the amount of albumin reabsorbed by the tubules (T_A) and the sieving coefficient. Comparison with the values assumed to be representative of the normal implicated increased glomerular permeability as the primary factor producing albuminuria. A decrease in the tubular capacity to reabsorb albumin was found to be a contributory factor.

The significance of the break observed in the $\frac{\Delta UV_A}{\Delta P_A}$ curve in nine patients is not altogether evident. It is suggested that the discontinuity of the curve reflects an increase in glomerular permeability as the plasma volume expands during the loading test.

The test was performed after hormonal therapy (ACTH or prednisone) on nineteen occasions in patients with amyloidosis and with the nephrotic syndrome. The most favorable response to treatment was either disappearance of albuminuria or a decrease in the slope of the curve; in a few cases a slight increase in the threshold and in T_A was observed, with no change in the slope. The decrease in the slope is interpreted as the result of a decrease in the hyperpermeability of the glomeruli. This effect was correlated with increased diuresis. An increase in the threshold and in T_A indicates improvement in the tubular reabsorptive capacity; however this change was of no apparent clinical benefit.

APPENDIX

Group I (Amyloidosis)

CASE 1. This thirty-three year old man had had pulmonary tuberculosis since 1952. The first symptoms of secondary amyloidosis had appeared in September,

1955. There was albuminuria, from 2 to 6 gm. daily. No signs of renal insufficiency were present at the time of this study.

CASE II. This forty-seven year old man was first admitted to the hospital in May, 1955, with dyspnea, edema, enlarged liver, distended neck veins and bilateral pleural effusion. Diagnosis at that time was possible constrictive pericarditis. The second admission was in March, 1956, for albuminuria of 12 to 20 gm. daily. Empyema of the pleural cavity was present. The patient died after air embolism. Pathological diagnosis was amyloidosis of the heart, lungs, kidneys and spleen.

CASE III. This sixty-three year old man had had pulmonary tuberculosis since 1950. Albuminuria and edema had appeared in March, 1956. On the first admission in June, 1956, the standard urea clearance was 18 cc./minute. Death occurred from circulatory collapse in June, 1956. Pathological findings included pulmonary tuberculosis; bronchogenic carcinoma; and renal, adrenal, splenic and hepatic amyloidosis.

CASE IV. In this twenty-nine year old man albuminuria had been known to be present since 1945. After tonsillitis in 1951 and, in 1956, acute respiratory infection followed by edema and puffiness of the face, he was admitted to the hospital in November, 1956, with a clinical diagnosis of glomerulonephritis entering the nephrotic stage. There was no hypertension, the glomerular filtration rate was normal. The patient was repeatedly treated with prednisone for five months without clinical benefit. He was readmitted in April, 1957, with severe diarrhea. Barium enema excluded tuberculous ileocolitis. The blood urea nitrogen was 25 mg. per cent. Pathological diagnosis was primary amyloidosis (heart, liver, kidneys and adrenals) associated with a nephrotic syndrome.

Group II (Nephrotic Syndrome)

CASE V. In this twenty-six year old woman albuminuria had been recognized fifteen months before admission. There was no past history of glomerulonephritis. Clinically she presented the typical picture of the nephrotic syndrome. On examination of urine only a few casts were found, no red or white cells. Antistreptolysin O titer was 100 units. ACTH given for ten days induced a 42 pound loss of water. Proteinuria disappeared. However the patient had a relapse six months later and was treated successfully with prednisone.

CASE VI. In this fifty year old woman albuminuria had been present since June, 1956, without a history of acute glomerulonephritis. Admission on January 18, 1957, showed puffiness, edema, moderate hypertension (185/100). The urea clearance was 37 per cent, an albuminuria of 9 gm. daily was noted. A first course of ten days of prednisone brought about clinical improvement and reduction in the proteinuria. The patient was treated with prednisone for five weeks, four days weekly; thereafter the albuminuria and edema entirely subsided.

CASE VII. This patient was a 75 year old woman. Since 1954 she had had edema of the ankles without any signs of cardiac insufficiency. She was admitted to the hospital in February, 1957. No hypertension, uremia, or pyelonephritis was evident. The serum proteins were markedly abnormal, with alpha$_2$-globulin increased to 38 per cent. The glomerular filtration rate was 47.8 cc./minute. No casts or red cells were present in the urinary sediment. Prednisone was administered without any clinical benefit. Clinical diagnosis was subacute glomerulonephritis in the nephrotic stage.

CASE VIII. This forty-one year old woman had been under treatment since 1952 as a case of "pure" nephrotic syndrome, without a past history of acute glomerulonephritis. No signs of renal insufficiency had appeared since that time. The patient was repeatedly treated with ACTH and prednisone. Two of three courses of treatment (either with ACTH or prednisone) generally resulted in complete resorption of the edema and reduced the proteinuria. The patient always relapsed within a few weeks.

CASE IX. This patient was a twenty-four year old woman. She had had an attack of acute glomerulonephritis in 1954. On June 21, 1956, severe edema and slight hypertension (170/100) were noted. The glomerular filtration rate was 36.8 cc./minute. Clinical diagnosis was subacute progressive glomerulonephritis in the nephrotic stage. No further examination has been obtained.

CASE X. The patient was a nineteen year old woman. There was a history of tonsillitis followed by acute glomerulonephritis in January 1955, followed by persistent albuminuria. The first admission to the hospital was in November, 1955. At that time her blood pressure was 170/110 mm. Hg; she had slight anemia, and the glomerular filtration rate was 37.8 cc./minute. Tonsillectomy was advised because of chronic infection and was followed by a slight decrease in proteinuria. Thereafter prednisone was administered with some benefit (glomerular filtration rate increased to 60.8 cc./minute). No follow up has been possible since March, 1956.

CASE XI. This thirty-eight year old woman had hyperthyroidism in 1948 which was treated with propylthiouracil. She had a relapse in 1956 which was treated only with rest. A few weeks later albuminuria was discovered. On admission the patient had no edema, hypertension or serum protein imbalance; albuminuria varied from 1 to 3 gm. daily. The tonsils

were infected. Streptococci group A were found on culture, but the plasma level of antistreptolysin O was normal. The glomerular filtration rate was 74 cc./minute. It was assumed that this patient suffered from residual albuminuria secondary to glomerulonephritis. Later she was treated with prednisone and the albuminuria was reduced.

CASE XII. In this twenty-three year old man albuminuria was discovered one month after an acute respiratory infection (January, 1955). However, he exhibited no edema, hypertension, or red or white cells in the urinary sediment. One year thereafter clinical signs of subacute glomerulonephritis were evident; at that time the urea clearance was reduced to 57 per cent of normal. During the following year renal insufficiency developed rapidly with progressive uremia. Death occurred on June 7, 1957. Pathological findings were subacute glomerulonephritis with enlarged pale kidneys, pulmonary edema and enlargement of the heart.

CASE XIII. In this fifty year old woman albuminuria was discovered in 1955. There was no history of acute glomerulonephritis. She was admitted to the hospital in September, 1956, with facial puffiness, chemosis, bilateral pleural effusion and edema; there was no hypertension or nitrogen retention. The first treatment with ACTH produced cardiac insufficiency secondary to water retention. Repeated courses of prednisone gave no dramatic improvement. However the patient slowly noticed reduction in edema and there was a slight decrease in proteinuria.

CASE XIV. This patient was a twenty-six year old man. In October, 1956, he had an acute illness followed by pain in the joints and moderate fever. In January, 1957, there was the first appearance of edema, with albuminuria of 17 gm. daily; no hypertension. The urea clearance was 103 per cent of normal. The antistreptolysin O titer was 50 units. Numerous hyalin and granular casts were found in the urinary sediment. Diagnosis was subacute progressive glomerulonephritis in the nephrotic stage. The first course of treatment with prednisone resulted in a weight loss of 14 pounds without marked increase in diuresis. The proteinuria was significantly reduced but only for two days, thereafter returning rapidly to its previous high levels. Signs of progressive renal insufficiency have developed within the past six months.

Group III (Severe Renal Insufficiency)

CASE XV. The patient was a seventy-one year old man. He had had an acute respiratory infection in November, 1954, followed by edema of the legs and puffiness of the face. Albuminuria was not recognized at that time. The first admission to the hospital was in August, 1955, with a diagnosis of subacute glomerulonephritis in the nephrotic stage. The blood pressure was 190/120 mm. Hg, blood urea nitrogen was 33 mg. per cent and standard urea clearance was 20.5 cc./minute. The blood cholesterol was 258 mg. per cent, blood proteins, 5.0 gm. per cent with 40 per cent albumin. The urinary sediment contained numerous red cells, granular and hyalin casts. There was an albuminuria of ± 2.5 gm. per day.

CASE XVI. In this twenty-nine year old woman acute post-tonsillitis glomerulonephritis was diagnosed in 1951. She had had a normal pregnancy in 1953. Since 1955, hypertension had been present; the blood urea nitrogen was 47 mg. per cent in December, 1955. A moderate anemia was noted. There was albuminuria of about 3 gm. per cent. Hemorrhagic and exudative lesions were noted in the eyegrounds. She had three other admissions in 1956, one with hypertensive encephalopathy (blood pressure 220/120 mm. Hg, blood urea nitrogen 48 mg. per cent). On each stay in the hospital, rest resulted in a decrease in the blood pressure levels. The renal insufficiency has not appeared to progress in the course of the last year.

CASE XVII. In this sixty-three year old woman diabetes was recognized in 1947 but required no insulin treatment. Since 1955 hypertension, edema and albuminuria have been noted. At the time of admission (January, 1956) a diagnosis of cardiac insufficiency was considered at first. After digitalisation the decrease in renal function and albuminuria persisted, although edema subsided. The final diagnosis was diabetes, hypertension, renal sclerosis or Kimmelstiel-Wilson syndrome, cardiac insufficiency.

CASE XVIII. In this forty-one year old man albuminuria was recognized in 1953 a few weeks after an acute episode with fever. He was admitted to the hospital on December 16, 1955, for digestive disturbances. On admission the blood pressure was 170/115 mm. Hg, blood urea nitrogen, 40 mg. per cent, standard urea clearance, 13 cc., inulin clearance, 18.8 cc./minute. No ocular changes were found. Diagnosis was chronic glomerulonephritis.

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Anuria Complicating the Treatment of Leukemia*

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IT is the purpose of this communication to report three cases of anuria in leukemia due wholly or in part to the increased excretion of uric acid complicating treatment. A review of the literature indicates that this complication is rarely reported and is very likely preventable.

In 1953 Gutman pointed out that "the turnover rate of endogenous nucleic acids is a critical factor in determining the rate of urate formation. This is relatively slow, particularly in respect to desoxyribonucleic acid in the healthy adult but evidently is greatly accelerated in certain diseases, notably in those of the hematopoietic system." [*1*].

Recent studies by Sandberg, Cartwright and Wintrobe have shown that the twenty-four-hour excretion of uric acid in acute lymphoblastic and myeloblastic leukemia, and in chronic myelogenous leukemia, is greatly increased as compared with the excretion in normal control subjects and in patients with chronic lymphatic leukemia [*2*]. These authors further showed that during the period when the leukocyte count falls following treatment with cortisone, amethopterin, or 6-mercaptopurine the uric acid excretion is further augmented. They stated that the mechanisms which might explain this action, making certain assumptions were: (1) the destruction of cells in the marrow, tissues and circulation, and (2) inhibition of the production of leukemic cells by interference with reutilization of catabolites to form new nucleic acids.

Weisberger found that the incidence of renal uric acid calculi in patients with leukemia was 4.7 per cent as compared with an incidence of 0.07 per cent in the general hospital population [*3*]. Since one-third of his patients with leukemia who had calculi had had no treatment other than antibiotics and blood transfusions, it is apparent that even without the use of therapeutic agents, there is increased stone formation.

In 1929 Bedrna and Polcák reported two cases of leukemia with ureteral block due to urate following x-ray therapy [*4*]. Increased blood levels and urinary excretion of uric acid were demonstrated. Both patients survived when the ureters were cleared by catheter. In the same year Jugenberg and Tschotschia suggested that kidneys involved with leukemic infiltrations excreted less uric acid, although the blood uric acid was increased following x-ray therapy [*5*]. None of their cases, however, appear to have been complicated by anuria or uremia.

Merrill reported three cases of uremia following x-ray therapy for leukemia in 1940 [*6*]. He recommended that renal function be evaluated carefully before treatment, that fluid intake be liberal, that the urine be alkalinized by giving sodium bicarbonate orally, and that the blood and urine uric acid be determined during and after x-ray treatment.

Since the advent of newer agents in the treatment of leukemia four cases of anuria or fatal uremia have been added to the literature [*7–10*]. These cases, together with Merrill's three and those to be given in detail in this report, are summarized in Table 1. Recently, as well as in the earlier literature, there are reports of treated patients with leukemia and crystalluria, stones, or lesser degrees of nitrogen retention, both with or without leukemic or non-leukemic renal disease [*3–6,11,12*].

A report of three new cases of leukemia in which anuria and uremia developed after treatment follows:

CASE 1. (No. 066715). P. H., a sixty-five year old woman, complained on October 17, 1951, of having had vague abdominal pain for four weeks. The systolic pressure was 130 mm. Hg, diastolic pressure 70 mm. Hg, and the pulse 84 per minute. The lymph nodes, liver and spleen were not enlarged. Urinalysis showed a specific gravity of 1.017, pH 6, and a trace of

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TABLE 1

ANURIA AND UREMIA COMPLICATING TREATMENT OF LEUKEMIA

Author, Year, Reference	Case No.	Age (yr.)	Type*	Blood Values before Treatment		Therapy	Leukocyte Count (per cu. mm.) Onset of Treatment / Onset of Uremia	Peak Blood		Cystoscopic Findings	Outcome	Autopsy
				Non-protein† Nitrogen (mg. %)	Uric Acid (mg. %)			Non-protein† Nitrogen (mg. %)	Uric Acid (mg. %)			
Merrill (1940), [6]	I	56	CM	52	...	X-ray	210,000 / 39,500	244	12.3	.....	Died	Bilateral packing of calyces with crystals and stones; mild pyelonephritis
.....	II	51	CL	43.7	...	X-ray	191,000 / 17,500	204	....	.....	Died	.....
.....	III	65	CM	(12)	...	X-ray	380,000 / 84,000	188	27.3	.....	Died	Gray inspissated material in renal pelves
Lear and Oppenheimer (1950), [7]	IV	61	CL	.....	...	Spray, x-ray	475,000 / 45,000	(55)	15.8	Uric acid crystals in bladder and protruding from ureterovesicle orifices	Died, diuresis; pylonephritis and septicemia	.....
Kravitz (1951), [8]	V	54	CM	(14)	...	Triethylene melamine	132,000 / 35,000	(140)	26	Uric acid crystals in bladder; right ureter blocked by "sand"	Diuresis, survived	.....
Hennemann (1955), (9)	VI	40	CM	.....	5.5	Urethane, x-ray	89,650 / 14,600	82	6.2	Uric acid crystals in bladder; ureteral findings not given	Died	Severe pyelonephritis with concretions in both pelves
McCrea (1955), [10]	VII	60	CM	(17)	...	Triethylene thiophosphoramid	740,000 / 39,000	(185)	10.4	Crystals in bladder; unable to enter ureters because of edema	Died	Ureters blocked by precipitate; pyramids were grossly "granular"
Kritzler (1957)	VIII	65	CM	(16.5)	6.1	Radioactive phosphorus	424,000 / 126,000	139 (92.5)	....	Clumps of uric acid crystals in bladder; ureters blocked 8 and 20 cm.; kidney pelvis (left) distended with gritty material	Diuresis, died	.....
.....	IX	65	CL	.....	...	Chlorambucil	347,000 / 26,000	(96)	9.8	Clumps of yellow crystals in bladder; ureter and pelvis distended with "chocolate mush"—chemically uric acid	Diuresis, survived	Biopsy of kidney, essentially normal; no leukemic infiltration or precipitate in tubules
.....	X	41	AL	88	...	Cortisone	540,000 / 48,000	194	38	Crystals in bladder. Kidney pelvis washings (10 per cent bicarbonate) returned clear; no flow from right; no obstruction found in ureter	Died	No precipitate in extrarenal urinary tract, leukemic infiltration of kidneys. Collecting tubules blocked with crystals

* CM = chronic myelogenous; CL = chronic lymphatic; AL = acute lymphatic leukemia.

† Figures in parentheses represent blood urea nitrogen determinations.

albumin. The hemoglobin was 11.0 gm. per 100 cu. cm.; erythrocytes, 3,900,000 per cu. mm.; leukocytes, 160,000 per cu. mm. The differential count was 26 per cent segmented neutrophils, twenty-five per cent stab forms, 14 per cent metamyelocytes, 20 per cent neutrophylic myelocytes, 1 per cent eosinophilic myelocytes, 1 per cent promyelocytes, 4 per cent blasts, 7 per cent lymphocytes, 1 per cent eosinophils and 1 per cent basophils. The platelet count was 153,000 per cu. mm. Bone marrow aspiration showed "a myeloid hyperplasia with a left shift similar to that of the peripheral blood picture." The serum uric acid was 6.1; calcium, 10.7; phosphorus, 3.6; and blood urea nitrogen, 16.5 mg. per 100 cu. cm. An intravenous pyelogram revealed good excretion of the dye bilaterally and mild nephroptosis. Radiographic examination of the stomach and small intestines revealed no abnormalities.

A diagnosis of chronic myeloid leukemia was made. No treatment was considered necessary at that time. A year later, October 23, 1952, iridectomy was performed at the Institute of Ophthalmology, New York, for secondary glaucoma due to an intraocular hemorrhage. At that time, there was no palpable enlargement of lymph nodes, liver or spleen. The hemoglobin was 10.1 gm. per 100 cu. cm.; erythrocytes, 4,100,000 per cu. mm.; leukocytes, 424,000 per cu. mm.; and platelets, 263,000 per cu. mm. The differential count was 84 per cent polymorphonuclear neutrophils, 11 per cent neutrophilic myelocytes, 1 per cent blasts, 3 per cent eosinophilic leukocytes, 1 per cent lymphocytes, and 2 nucleated erythrocytes per 100 leukocytes.

On November 6, 1952, 7.94 millicuries of radioactive phosphorus was administered to the patient orally. The leukocyte count on November 19 was 168,000 per cu. mm. Two days later the patient complained of pain in the left flank, and hematuria developed. The output of urine on November 23 was 8 cu. cm. and on November 24, 2 cu. cm. The total fluid intake, first measured on November 22, was 1,100 cu. cm. in twenty-four hours. The fluid intake from November 23 to 27 averaged between 1,500 and 2,000 cu. cm. and was almost all parenteral. Cystoscopic examination of the bladder on November 25 revealed no abnormalities. The ureteral catheter could not be passed beyond a point half way to the kidney on the left, nor beyond a point near the kidney on the right. A ureterogram was interpreted as showing no filling above the tip of the catheter on the right and mild hydronephrosis with blunting of the calyces on the left. On November 25 the serum carbon dioxide was 18.3; chloride, 97; potassium, 7.3; and sodium, 115 mEq. per L. The serum non-protein nitrogen was 139 mg. per 100 cu. cm. The electrocardiogram revealed tall, peaked T waves. Fifteen cubic centimeters of 10 per cent sodium salt of a carboxylic resin was administered as a colonic rinse. Fifty grams of the resin suspended in 300 cu. cm. of water was then given by rectal tube and repeated the next day when the serum potassium had fallen to 5.2, the sodium to 121.2 mEq. per L. The daily output of urine from November 25 to 27 averaged 124 cu. cm. On November 27, clumps of pale yellow material were found in the bladder, and both ureters were blocked. A left nephrostomy and pyelostomy were performed. The ureter and pelvis was described as full and gritty. During the three postoperative days fluid intake of between 2,500 and 3,000 cu. cm. was maintained. The serum sodium rose to 140.7 mEq. per L., and the potassium dropped to 2.2 mEq. per L. as urinary output rose from 660 cu. cm. on the third postoperative day. The patient, however, lapsed into coma and the temperature rose in the last twenty-four hours to 106°F. The question of intracerebral hemorrhage was entertained as a final cause of death but an autopsy was not obtained.

Comment: Anuria and uremia were due to block of the ureters and renal pelves by urates excreted in increased amounts, presumably as a consequence of treatment with radioactive phosphorus. Fluid intake at the time of treatment was not sufficient. Leukemic infiltration of the kidneys and other renal disease were not excluded anatomically; however, such possibilities seem remote, since the pretreatment blood urea nitrogen was normal. A diuresis followed pyelostomy. The precise cause of death was not clear.

Case II. No. 162979. P. H., a sixty-three year old man, was first seen in the Vanderbilt Clinic in December, 1953. A diagnosis of chronic lymphatic leukemia had been made elsewhere three years previously. There was generalized lymphadenopathy and hepatosplenomegaly. The hemoglobin was 9.5 gm. per 100 cu. cm.; erythrocytes, 3,160,000 per cu. mm.; leukocytes, 859,000 per cu mm.; and platelets, 85,000 per cu. mm. In the differential count there were 91 per cent lymphocytes, 1 per cent neutrophils, and 8 per cent myeloblasts.

Two and one half milligrams of triethylene melamine (TEM) was given orally on two successive days. Within seven days the leukocyte count was 125,000 per cu. mm. Five milligrams of TEM were given on February 16, 1954 when the leukocyte count was 225,000 per cu. mm., and again on March 2, 1954 when the leukocyte count was 175,000 per cu. mm. Two weeks later the leukocyte count had fallen to 20,000 per cu. mm. There was no untoward effect.

In November 1954 the lymph nodes averaged 2 to 3 cm. in diameter. The liver and spleen were not palpable. The leukocyte count was 357,000 per cu. mm. Two hundred and twelve milligrams of CB 1348 (p-di-(2-chloro-ethyl)-aminophenyl butyric acid) (chlorambucil) was administered over a period of

twenty-four days. The lymph nodes became smaller, and the leukocyte count was 115,000 per cu. mm. On April 4, 1955, another course of chlorambucil was started. Between April 4 and June 28 the patient received 340 mg. The leukocyte count fell gradually from 347,000 per cu. mm. to 80,000 per cu. mm. on June 14, and to 19,000 per cu. mm. on June 28.

About July 1, during a heat spell, the patient became oliguric. On July 5 hematuria was noted and on the next day there was pain in the left flank. Only a few drops of sanguineous fluid were voided in twelve hours. He then reported to the clinic and was admitted to the hospital.

The liver was felt 4 cm. below the right costal margin, and the spleen tip 2 cm. below the left costal margin. The leukocyte count was 26,250 per cu. mm., the hemoglobin 12 gm. per 100 cu. cm. and the platelet count 80,000 per cu. mm. A few cubic centimeters of urine removed by catheter were acid and loaded with erythrocytes. The output of urine during the next three days averaged 40 cu. cm. Fluid intake on July 7 was 1,000 cu. cm., on July 8, 650 cu. cm. and on July 9, 900 cu. cm. On July 8 the blood urea nitrogen was 71 and uric acid 9.8 mg. per 100 cu. cm. The serum CO_2 was 17.8; chloride, 100; sodium, 133; and potassium, 6.3 mEq. per L. Intravenous pyelogram revealed no excretion on the left and very scant excretion on the right. On July 9 the urea nitrogen was 96 mg. per 100 cu. cm. At cystoscopic examination on July 9, 5 cu. cm. of sanguineous urine containing flakes of yellow crystals were found in the bladder. The bladder mucosa was described as hemorrhagic and bullous. Later in the day a doubly intubated right ureterostomy and nephrostomy were performed. The ureter was bifid proximally and distended with "chocolate colored mush." One small aliquot of this material was found chemically to be uric acid. A biopsy specimen of the kidney was obtained. No significant abnormalities were found histologically. There was no leukemic infiltrate nor was any precipitation of urates present in the tubules.

During the first eight postoperative hours the urinary output was 600 cu. cm. Despite some postoperative urinary infection the output remained good. On July 26 the blood urea nitrogen was 27 mg. per cent and uric acid 4.4 mg. per cent. Intravenous pyelogram revealed good excretion of dye bilaterally and the patient was discharged. On November 4 the leukocyte count was 38,000 per cu. mm. and the blood uric acid 9.8 mg. per 100 cu. cm.

The leukocyte count rose gradually during the next six months. The patient was readmitted for treatment in May 1956, at which time the leukocyte count was 159,000 per cu. mm.; the hemoglobin, 10.2 gm. per 100 cu. cm.; and the blood uric acid, 5.9 mg. per 100 cu. cm. The liver edge was felt 4 cm. below the costal margin, the spleen tip 2 cm. Five milligrams of chlorambucil was administered daily for twenty-five days. The twenty-four-hour fluid intake was kept between 5 and 6 L. The leukocyte count fell gradually to 9,700 per cu. mm. No uric acid crystals were found in the urine. The blood urea nitrogen rose to 31 mg. per cent; the output however, remained above normal. The maximum blood uric acid was 5.9 mg. per cent. Since discharge on May 22, the patient has been regulated on small doses of chlorambucil without complication.

Comment: Anuria and moderately severe uremia occurred during the tenth week of a gradual fall in leukocytes while chlorambucil was given. Diuresis and recovery followed ureteronephrostomy and removal of urate precipitate on one side. An underlying leukemic or non-leukemic renal failure appears to have been excluded by the fact that prior to the episode of anuria the patient received a course of TEM without renal complications, and later when a course of chlorambucil was repeated with full fluid intake there was no oliguria, crystalluria or significant rise of the blood urea nitrogen from a high normal pretreatment level. The anuria is considered to have been a complication of therapy probably precipitated by dehydration due to hot weather.

[Case III. No. 18455. A forty-one year old woman was admitted to the Valley Hospital, Ridgewood, New Jersey on June 7, 1955, complaining of sore throat, fever, malaise and intermittent nausea and vomiting of three weeks' duration. Just prior to admission easy bruising and bleeding developed at the gingival margins. The systolic blood pressure was 116 mm. Hg, and diastolic pressure 82. The temperature was 104°F. The patient was acutely ill and nauseated. The sclerae were icteric. There was minimal bleeding of the gum margins. Petechial hemorrhages were noted on the palate, the buccal mucosa and on large, gray tonsils. The lymph nodes were moderately and generally enlarged. The spleen tip was felt 4 cm. below the costal margin and the liver 3 cm. below the costal margin. There were widespread ecchymoses of the skin and purpura of the arms and legs.

The hemoglobin was 13.8 gm. per 100 cu. cm.; the leukocytes, 540,000 per cu. mm.; and platelets, 19,000 per cu. mm. In the differential count large lymphocytes constituted 77 per cent; monocytes, 5 per cent; segmented neutrophils, 3 per cent; and blasts, 15 per cent of the cells. The urine was acid, its specific gravity 1.010; no glucose, albumin, urobilinogen, bile, or formed elements were noted. The serum bilirubin was 1.1 mg. per cent; thymol turbidity test, 1.5 units; prothrombin time, 32.5 seconds (normal control 14.4 seconds); blood sugar, 145 mg. per cent; non-protein nitrogen, 84 mg. per cent; and the

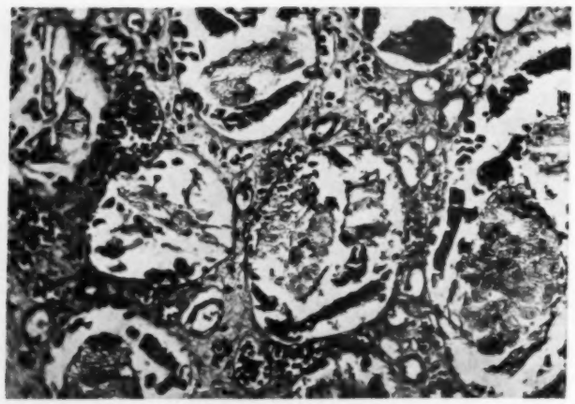

FIG. 1. Case x. Photomicrograph of a section of a pyramid of kidney. Hematoxylin and eosin stain. The collecting tubules are blocked with urate precipitate.

cephalin flocculation test, 2 plus. Radiographic examinations of the chest and abdomen revealed no abnormalities other than an enlarged liver and spleen. The bone marrow examined by aspiration was cellular and similar to the peripheral blood smear. Temperature was 101° to 102°F. during the first two days of hospitalization. During this time she vomited twice.

On the third and fourth days after admission the patient received 800 mg. of cortisone a day. Within twenty-four hours after treatment was started the patient became oliguric, and in the second twenty-four hours she was anuric. The leukocyte count forty-eight hours after treatment was started was 41,800 per cu. mm. One hundred fifty cubic centimeters of urine, removed from the bladder by catheter on the third day after treatment was started, was acid and loaded with erythrocytes; the specific gravity was 1.009, the albumin was 3 plus, with a trace of glucose. On the same day the serum non-protein nitrogen was 194 and the serum uric acid 35 mg. per cent. The carbon dioxide was 24 volumes per cent and the serum chloride 84.5 mEq. per L.

The fluid intake was largely parenteral M/6 lactate and averaged 1,850 cu. cm. a day. The urinary output was less than 50 cu. cm. a day. Administration of cortisone was decreased to 50 mg. a day. On the sixth day after treatment was started the serum non-protein nitrogen was 246 mg. per cent; uric acid, 38 mg. per cent; carbon dioxide combining power, 72 volumes per cent; and cholrides, 70.5 mEq. per L. Cystoscopic examination revealed 200 cu. cm. of dark fluid in the bladder. No crystals were described. A catheter was passed to the right renal pelvis. No fluid could be obtained. Small washings of sodium bicarbonate were returned clear. Watery diarrhea and generalized twitching developed and the patient died on the seventh day after treatment was started.

The autopsy findings included the following: the lymph nodes were small. Cutaneous and serous surface hemorrhages were present, with 500 cu. cm. of pink fluid in the peritoneal cavity. The spleen weighed 475 gm. The kidneys weighed 240 and 270 gm. Yellow streaks were seen on the cut surface of the renal pyramids. No crystals or precipitate were described in the calyces, ureters or bladder. Microscopic examination revealed widespread leukemic infiltration of many organs and of the kidneys. Most of the collecting tubules were impacted with crystalline and amorphous material compatible with urate precipitate. (Fig. 1.)

Comment: In this case a number of factors contributed to the development of acute anuria. At the time treatment was begun there had been high fever and vomiting. The pretreatment serum non-protein nitrogen elevation was probably due in part to dehydration and in part to renal insufficiency associated with leukemic infiltration of the kidney. The recorded fluid intake during the first days of cortisone treatment appeared to be inadequate. The fall of circulatory leukocytes from a high level was extraordinarily precipitous. Under such circumstances the twenty-four hour uric acid excretion may be six times normal. The blood uric acid level reached 35 mg. per 100 cu. cm.

The case is unusual in two other respects: (1) no other case of acute leukemia was found in the literature with anuria complicating treatment and (2) it is the only recorded instance of leukemia in which the urinary block is in the renal tubules rather than in the pelvis or ureters. Obstruction of the renal collecting tubules by urates was found by Weisberger in a case of lymphosarcoma in which greatly enlarged liver, spleen and lymph nodes were no longer palpable three days after a single dose of nitrogen mustard [*3*]. Anuria and uremia developed. The serum uric acid rose to 36 mg. per cent. At autopsy the obstruction was in the renal tubules. No extrarenal urinary tract obstruction by urate was found.

COMMENTS

The three cases herein described and those recorded in the literature in which treatment was complicated by anuria and uremia are summarized in Table 1. All but two of the patients were over fifty years of age. Anuria following treatment may occur without prior evidence of impaired renal function. Pretreatment blood non-protein nitrogen or urea nitrogen levels were normal in five of the seven cases in which it was determined.

Leukemic infiltrates of the kidney may be presumed to be a cause of renal insufficiency in

some cases. Since three of five patients in whom the kidneys were examined microscopically showed no infiltrates, leukemic involvement of the kidneys is not a necessary feature of the syndrome.

Nine of ten patients had chronic leukemia (six myeloid, three lymphatic). Sandberg et al. showed that the excretion of uric acid in untreated patients with chronic myelogenous leukemia may be as much as two and a half times that of either normal control subjects or untreated chronic lymphatic leukemia [*2*].

In all instances the number of circulating leukocytes was high before treatment was begun and very considerably lower at the onset of anuria. The interval from the beginning of treatment to the development of oliguria was short in some cases (two to three days) and long (sixty-two days) in others. The mortality of this complication is high; only two patients survived. Two others (Cases IV, VIII) died despite diuresis.

Obstruction of the extrarenal urinary tract by urate precipitate was demonstrated clinically or at autopsy in eight of the cases. Removal of this block can be attempted either by ureteroscopic lavage or pyelostomy. In Cases IV and V diuresis followed lavage of both ureters by means of ureteral catheters which were left in place overnight. Recurrent obstruction was repeatedly but not finally overcome by this means in Hennemann's case [*9*]. In Case VII this method failed. Diuresis, however, occurred when lavage and drainage were carried out by nephrostomy and pyelostomy on one side. In Case IX ureterostomy was followed by diuresis and subsidence of uremia. It would appear that lavage of both ureters by catheterization from below should be tried first, and if this fails, nephrostomy must be performed.

Blockage of the renal tubules in anuria cannot be recognized clinically except by failure of the surgeon to demonstrate urate deposits in the calyces, ureters or bladder. There is no direct approach to the problem of tubular block by urates at this time.

Management of the sequela of the anuria is directed toward adequate but carefully limited fluid intake (1,200 to 1,500 cu. cm. a day). Sixth molar lactate or bicarbonate is used cautiously for acidosis. The routine use of alkali administered orally or parenterally to "dissolve crystals" in the urinary tract is dangerous and ineffective in the anuric patient.

Prevention of this rare complication deserves emphasis. In none of the cases summarized could it be determined that the fluid intake was 3 to 4 L. per day at the time of treatment. It can be seen in the protocol of Case IX that when an antileukemic agent was used cautiously again after the episode of anuria and fluids were forced, the output of urine was maintained and there was only a minimal rise in blood nonprotein nitrogen. The fall in white cells was less dramatic.

Fluids are forced to increase urine volume and thus dilute the urinary urate and other substances which may contribute to the precipitate. This is done when the pretreatment blood uric acid level is normal as well as when it is elevated, since a normal blood level does not preclude the presence of a greatly increased urinary rate of excretion of uric acid. In this series anuria occurred in some cases when the pretreatment blood uric acid level was normal.

Pretreatment appraisal of renal function has been emphasized as desirable. However, it is not known whether or not renal insufficiency increases the risk of stone formation. This series includes cases in which no renal insufficiency was demonstrated by ordinary appraisal before treatment. It would seem safe to force fluids in such patients in whom the urate excretory load may be expected to be high and a high urine output can be maintained.

In most patients with leukemia in whom response to therapy was good oliguria or anuria did not develop. However, the serious nature of these rare complications justifies such a simple preventive approach in all patients treated.

It is probable that the risk of extrarenal blockage by precipitate may also be reduced by the cautious use of antileukemic agents when the circulating leukocyte count is high. Whether or not this precaution is necessary when a large urine volume is maintained may be questioned. However, a precipitous drop in circulating leukocytes appears to be contributory in most of the cases.

The usefulness of administration of sodium bicarbonate with antileukemic agents to raise urine pH and thus to increase urate solubility, first suggested by Merrill and re-emphasized by others, remains controversial. Administration of 12 gm. of sodium bicarbonate a day were found by Flippin and Reinhold in 154 samplings to give an average urine pH of 7.14 [*13*]. When 6 gm. were given the average pH of the urine was 6.27. It is not known whether such levels

prevent the formation of urate calculi. Moreover, the change in urine pH depends on the normality of renal tubular function, which may be impaired in some patients with leukemia who are undergoing treatment. It is reasonable to conclude that the large amount of sodium bicarbonate needed to effect a moderate increase in urine pH is not justified or practical, and may carry a risk in some cases.

SUMMARY

Nine cases of chronic and one of acute leukemia in which treatment by almost all the established antileukemic agents was complicated by extra- or intrarenal block due to urate precipitate are summarized. Only two of the nine patients survived.

Factors contributory to the development of this rare complication of therapy are (1) age, the fifth and sixth decades, (2) the high urinary output of urate and tendency to calculus formation in the untreated patient with leukemia, (3) further increase of urinary urate excretion due to destruction of large numbers of leukocytes or to inhibition of the formation of leukocytes and associated incorporation of purines by the therapeutic agent, and (4) dehydration and inadequate volume of urine.

Ureteropelvic blockage may be relieved by a determined effort at lavage with ureteral catheterization or, if this fails, by lavage after nephrostomy or ureterostomy. Full hydration with maintenance of a high output of urine during treatment is the most practical and effective preventive measure.

Although this complication of leukemia is rare, it may be catastrophic. It is advisable to recommend a high fluid intake to all patients with leukemia during the first few weeks of any kind of therapy directed toward reduction of the mass of the leukemic cells.

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Application of Corrected Electrocardiographic Lead Systems in Man*

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CONCEPTS of electrocardiographic theory have changed considerably in recent years [*1–12*]. Research has resulted mainly in the design of improved electrocardiographic lead systems based on sound physical principles. Since these lead systems have been developed using models of the human torso, demonstration of their reliability and accuracy in living subjects is necessary before they can be recommended for general clinical use. This is the report of a comprehensive study that compares the new lead systems with older conventional systems in normal subjects and in patients with heart disease.

Several simplifying assumptions have been made in the past in regard to electrocardiographic theory. These assumptions have been retained in most methods of vector analysis which gained popularity in recent years, although their validity has not been proved. One such assumption has been the treatment of anatomic lead axes as though they were electrical lead axes. However, this assumption is valid only when the following requirements are fulfilled: (1) The human body as a volume conductor is of regular shape (ideally a sphere or at least a cylinder); (2) the resistivity of all body tissues is homogeneous; and (3) the electrical center of the heart or the heart dipole equivalent is fixed, point-like and *centrally* located in the volume conductor.

As these simplifying assumptions are obviously not fulfilled for the human body, research has been directed toward quantitative determinations of the sources of error and of the means for correcting them. In independent studies, Burger and van Milaan [*1–3*], Schmitt and Simonson [*4–5*], Frank [*6–9*], and McFee and Johnston [*10–12*], arrived at almost identical conclusions. These have considerably enlarged our knowledge of the electrophysiology of the heart.

Experiments were performed on torso models of homogeneous conductivity shaped after different types of body build. An artificial dipole that simulated the physiological current source of the living heart was shifted through the heart region. Recordings were taken from a large number of leads on the model surface. The characteristics of a lead were defined in terms of *lead strength* and *lead direction*. These two parameters are most conveniently expressed as a vector for each lead. Such a vector has been termed "lead vector" by Burger and van Milaan [*1–3*], "lead transfer impedance" by Schmitt and Simonson [*4,5*], "image vector" by Frank [*9*], "lead field vector" by McFee and Johnston [*10–12*], and "effective lead axis" by Schaffer [*13*]. (The latter term will be used throughout this paper.) These entities are either identical or closely related to each other mathematically.

It was soon found that effective lead axes do not coincide with anatomic lead axes. The direction of a lead could not be predicted from the site of electrode application. The angular discrepancies between anatomic and effective lead axes were as much as 45° in limb leads and 56° in precordial leads with large variations [*4,5*].

Lead strength was determined as the ratio between the magnitude of the current source and the amplitude of the recorded deflection in a lead. The conventional leads exhibited a wide scatter of lead strength.

Eccentricity (off center location) *of the heart* in

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the volume conductor was found to be the main source of error for the skewness of effective lead axes in conventional systems. Differences in body build [*14,15*], and tissue conductivity [*16*] seemed to exert less influence on effective lead axes.

After collecting data on a large number of leads from the surface of the torso models, attention was directed toward the design of improved leads that would fulfill the following two requirements: (1) Accuracy in direction of effective lead axes. (This direction should be maintained for the variety of heart dipole positions encountered in different subjects with varying torso shapes and heart positions.) (2) Equal lead strength for all leads. (This would permit amplitude measurements that are comparable from one lead to another and at the same time make those leads suitable for vectorcardiography.)

Electromotive forces in three-dimensional space are most conveniently displayed for analysis by an orthogonal lead system of three leads, each perpendicular to the others. Three basic leads, therefore, were designed, one each in the horizontal (X), vertical (Y) and sagittal (Z) directions. Lead corrections were accomplished by combinations of leads and the use of appropriate resistor circuits in order to counterbalance skew producing and contaminating electromotive forces.* Thus it was possible to devise corrected, orthogonal leads which, at least in torso models, showed only minor deviations from the ideal [*4,8*].

Schmitt and Simonson [*4*], proposed the use of fourteen electrodes for the three orthogonal leads. This number represents the upper limit of practicality. Frank [*8*] used seven electrodes for the same leads, the theoretical minimum for first-order lead corrections. Reynolds and his co-workers [*17*] advocated lead grids with up to sixty-three electrodes for one lead. Helm [*18*] used a completely different approach by introducing sponge rubber sheets as electrodes.

Quantitative experiments comparable to those in torso models are not feasible in man. Before the use of corrected orthogonal leads can be recommended for clinical use, however, evidence should be presented that answers the following questions: (1) Are the data obtained in artificial models valid to the same extent in living man? (2) Are the characteristics of corrected leads the same in normal subjects and in patients with heart disease? (3) Is the use of these systems practical in routine application?

Present experimental methods do not permit a direct approach to these problems. An indirect approach, therefore, was used in the present study. Torso model data on corrected and conventional leads are available from the publications quoted previously. Their discrepancies in models are known. If the findings in models apply to man, the discrepancies between recordings taken with corrected and conventional lead systems should have the same dimensions as in torso model studies. Furthermore, if the lead corrections made are accurate, then tracings taken with different corrected lead systems should give identical (or at least very similar) results, whereas conventional systems should not. Since the corrections used in the proposed systems differ greatly in design and location of electrode placement, a close resemblance could hardly be considered coincidental.

In the present study, conventional vectorcardiographic leads were chosen for comparison rather than conventional electrocardiographic leads. Directions of instantaneous vectors can be read directly from vectorcardiograms, but have to be constructed when scalar electrocardiographic leads are used. In addition, time phase relationships are displayed more accurately in the vectorcardiograms since electronic methods are used.

Therefore, in the present study a quantitative correlation was performed using two corrected lead systems (Schmitt [*4*] and Frank [*8*] and two conventional vectorcardiographic systems tetrahedron [*19*] and cube [*20*]). Bipolar and unipolar leads are used in the two latter systems. Standard leads I and VF are applied for recordings of the frontal plane of Wilson's tetrahedron. Results obtained in this plane, therefore, can be taken as representative of standard electrocardiographic limb leads [*21*].

MATERIALS AND METHODS

The four lead systems mentioned previously were applied consecutively to forty normal subjects and fifteen patients with a variety of heart disease. All subjects had complete clinical studies including a twelve lead electrocardiogram.

The tracings were photographed* from a cathode-

* For more detail of lead design the reader is referred to the publications of Schmitt and Simonson [*4,5*], Frank [*8*], Reynolds and his associates [*17*], and Helm [*18*].

* Oscilloscope camera, Maurice LeCover, 1976 Talmadge Street, Los Angeles 27, California.

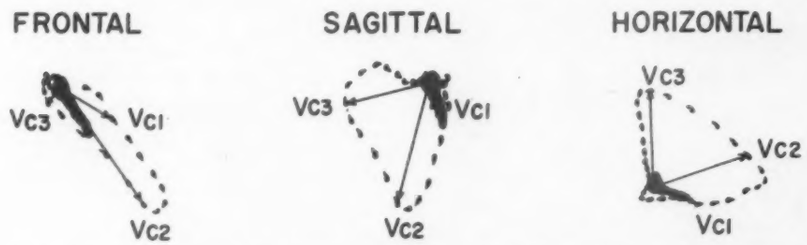

FIG. 1. Vc 1, Vc 2 and Vc 3 represent instantaneous vectors in the early, middle and late portions of QRS. For each subject comparable vectors were identified in the tracings of the four tested lead systems (see text). This allowed a comparison of different phases of QRS.

ray oscilloscope.* Preamplifiers† with an input impedance of 20 megohms and a flat frequency response from 0.1 to 10,000 cycles per second, were used. Scalar leads of all systems were recorded with a constant time reference lead, using an electronic switch.‡ Loops and scalar leads were recorded on 5 inch photographic paper.§ Drop-shaded time-markings of the loops were set at 400 per second.‖

All records were obtained with the subject in the supine position. The fifth intercostal space was taken as the horizontal level for the application of the chest electrodes in Frank's system, as advocated by the author [*8*].

Records of loops of all systems were taken in the frontal, right sagittal and horizontal planes. Three instantaneous vectors of each subject were selected in the early, middle and late portions of QRS. (Fig. 1.) These instantaneous vectors were determined for all systems. Characteristic irregularities in loop configuration which were common to all systems in a given subject were taken as landmarks. Once a common instantaneous vector for one subject was identified other common instantaneous vectors could be determined using the time markings. Since the scalar magnitude of every instantaneous vector can be determined twice from three planar projections, an average was used when differences were found. All records that showed discrepancies of more than 4 mm. on the 5 inch films were discarded. The same was done when the identification of instantaneous vectors was not possible. (This occurred in thirteen cases that were then not included in this report.) Schmitt's SVEC III system [*4*] was chosen as the reference system for all correlations because it exhibited the least sensitivity to dipole position variations in model experiments.

* Cathode-ray oscilloscope, type 304 A, Allen B. DuMont Laboratory Inc., Clifton, New Jersey.

† Preamplifiers, type 122 (modified for the low frequency range), Tektronix, Inc., Portland 7, Oregon.

‡ Electronic switch, type 330, Allen B. DuMont Laboratory Inc., Clifton, New Jersey.

§ Lino Writ 3, Type B, E. I. DuPont de Nemours and Company Inc., Wilmington 98, Delaware.

‖ VCG Oscillator, Electro-Medical Engineering Company, 2317-A West Olive Avenue, Burbank, California.

Angular deviations were determined between the reference system and the compared systems for each of the selected instantaneous vectors in each plane (e. g., angle formed by Vc 1 of the SVEC III and Vc 1 of one of the compared systems). The deviations were designated positive when clockwise and negative when counterclockwise. An angular scale from 0 degree to 360 degrees was used for each plane, 0 degree being always to the right of the observer with a clockwise sequence.

Relative lead strength was calculated from the equations:

$$X_c = K\,X_{SVEC}$$
$$Y_c = K\,Y_{SVEC}$$
$$Z_c = K\,Z_{SVEC}$$

X_{SVEC}, Y_{SVEC}, Z_{SVEC}, indicate the scalar magnitudes of the selected instantaneous vectors as recorded by the SVEC III system. X_c, Y_c, Z_c, represent scalar magnitudes of the same instantaneous vectors in one of the compared systems. Equations were solved for the factor K representing the magnitude ratio of the compared systems with the SVEC III.

RESULTS

Relative Lead Strength. Data for all instantaneous vectors of the early, middle and late portions of QRS were pooled in order to obtain results representative of the whole QRS cycle. Results are given in Table I, in which the lead strength of the reference system (SVEC III) was taken as 1.0 for all leads. The lead strength of Schmitt's SVEC III system exceeded all other systems, Frank's being second in the correlation. The range of findings for relative lead strength was found to be larger in man than that reported from models [*4*].

The relative lead strength data differed markedly from one system to another. A comparison of the different systems could be made only when the results of relative lead strength determinations were plotted on a comparable level. The mean values for lead X of each system,

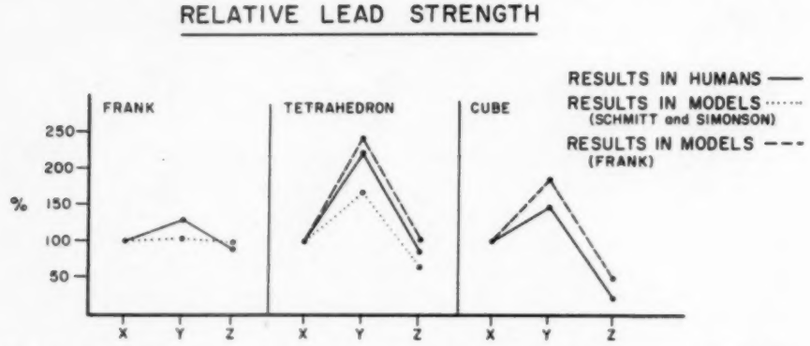

FIG. 2. Correlation of relative lead strength of the four lead systems studied. The results obtained in man are plotted in relation to Schmitt's SVEC III system in which the lead strength for all leads was taken as 100 per cent. The results reported from studies in torso models by Schmitt and Simonson, [*4*] and Frank [*22*] are plotted in relation to ideal (100 per cent for all leads). The relative lead strength of lead X was taken as 100 per cent for all systems in order to raise the results obtained by different systems to a comparable level (see text).

TABLE 1

RELATIVE LEAD STRENGTH CORRELATION. SUMMATED RESULTS INCLUDING VECTOR GROUPS 1, 2 AND 3 (SEE TEXT). FIGURES REPRESENT AMPLITUDE RATIOS BETWEEN COMPARED SYSTEMS AND SCHMITT'S CORRECTED SYSTEM. AMPLITUDE DATA OF THE LATTER SYSTEM WERE TAKEN AS 1.0 FOR EACH LEAD. NOTE THAT THE LEAD STRENGTH WAS HIGHEST FOR SCHMITT'S SYSTEM, SMALLEST FOR THE TWO CONVENTIONAL SYSTEMS

	X	Y	Z
Frank			
Mean	0.64	0.83	0.56
Standard deviation	0.41	0.44	0.46
Standard error	0.04	0.04	0.04
Tetrahedron			
Mean	0.13	0.29	0.11
Standard deviation	0.17	0.27	0.21
Standard error	0.02	0.03	0.02
Cube			
Mean	0.40	0.59	0.09
Standard deviation	0.42	0.44	0.40
Standard error	0.04	0.04	0.04

therefore, were designated arbitrarily as 100 per cent. (Fig. 2.) The multiplication factor used for lead X in order to obtain 100 then was applied to the relative lead strength values for leads Y and Z. In this fashion all mean results in Table 1 could be raised to the higher level of the reference system for comparison. The same procedure was applied, also, to the lead strength data reported from studies of torso models [*4,22*]. Figure 2 includes therefore: (1) The percentage deviations of relative lead strength of all compared systems from the corrected reference system as found in man. (In this latter system the lead strength was taken as 100 per cent for all leads.) (2) Analogous percentage deviations of the same lead systems from ideal as reported from experiments with models. In the latter case, 100 per cent was taken as the level of ideal for all three leads. In this fashion the discrepancies between conventional leads and Schmitt's corrected leads in man could be demonstrated, together with the discrepancies between the same conventional leads and ideal as found in models. It was mentioned previously that the relative lead strength of a lead is a function of absolute lead strength *and* effective lead direction. The correlation in Figure 2 includes all parameters of a lead.

The results in man of relative lead strength for the tetrahedron were found to be in between the results in models of Schmitt [*4*] and Frank [*22*]. A very close relationship between the lead strength data in man and Frank's results in models [*22*] was also found for the cube system.

The relative lead strength results obtained with Frank's system deviated least from the reference system. When lead strength data of different phases of QRS were compared, variations were found, but differences were not significant statistically.

Angular Deviations. Angular discrepancies between different systems in any one of the three

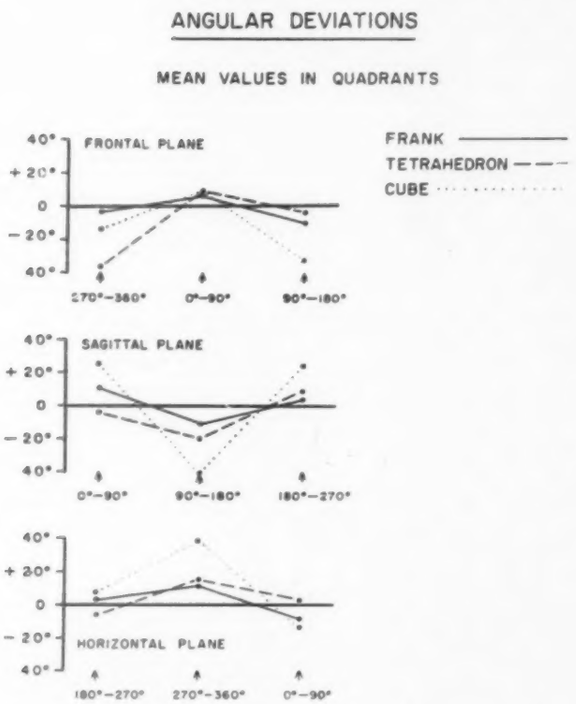

FIG. 3. Mean angular deviations of instantaneous vectors from the corrected reference system (SVEC III). The instantaneous vectors were grouped arbitrarily in quadrants of 90 degrees in each plane. As angular deviations from the reference system depend on the direction of instantaneous vectors, the grouping according to quadrants led to more homogeneous groups. Note the close relationship between the two corrected systems and the larger discrepancies of the conventional systems.

planes (frontal, sagittal or horizontal) depend on four factors: (1) The direction of the effective lead axes of the compared systems; (2) the strength of the leads; (3) the contaminations by forces which do not belong to the plane proper; and (4) the angle between the instantaneous vectors and the effective lead axes.

It follows from the last factor that angular deviations of different instantaneous vectors depend on their direction. Therefore, these vectors were grouped arbitrarily in quadrants of 90 degrees in each plane to facilitate comparison of results obtained by different systems. Mean results of angular deviations from the reference system are given in Figure 3. In all planes the mean angular deviations of Frank's corrected system from Schmitt's SVEC III were of minor degree only. The discrepancies between the conventional systems and the two corrected systems were marked. This was especially so for the cube system.

Angular discrepancies for the total of instantaneous vectors and for the vectors grouped according to time are shown in Figure 4. The

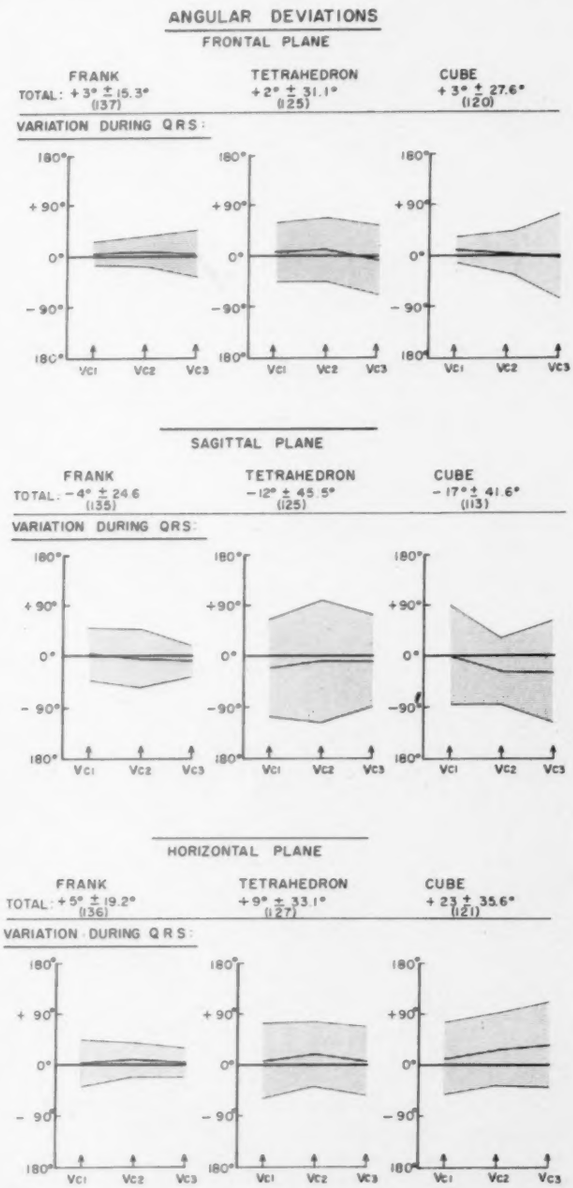

FIG. 4. Mean angular deviations and ranges of instantaneous vectors from the reference system (SVEC III). The vectors were grouped according to time for each plane. The figures on top of each plane indicate the mean and standard deviations for the total of instantaneous vectors of each plane (Vc group 1^+ 2^+ 3). The number of instantaneous vectors is given in parenthesis. The solid lines on the diagram indicate the mean angular deviations. The shaded area represents the range of findings (twice the standard deviation on each side of the mean). Note the larger ranges of findings for the conventional systems. The marked changes of ranges during QRS suggest contaminations by forces not belonging to the plane proper (see text).

TABLE II

ANGULAR VARIABILITY FOR EACH SUBJECT AND EACH PLANE WAS DETERMINED AS DESCRIBED IN THE TEXT. MEAN ANGULAR VARIABILITY PER SUBJECT FOR EACH OF THE COMPARED SYSTEMS IN EACH PLANE IS GIVEN IN THIS TABLE. THE MAXIMAL ANGULAR VARIABILITY WAS CALCULATED FROM FRANK'S TORSO MODEL DATA (SEE TEXT). NOTE THE HIGH PERCENTAGE OF SUBJECTS EXCEEDING THE MAXIMAL CALCULATED RANGE

	Frank	Tetrahedron			Cube		
	Angular Variability (in man)	Angular Variability (in man)	Maximal Angular Variability (calculated)	Cases Exceeding Calculated Range (%)	Angular Variability (in man)	Maximal Angular Variability (calculated)	Cases Exceeding Calculated Range (%)
Frontal							
Mean	22°	37°	52°	26	36°	43°	28
Standard deviation	16.1	32.9	...	..	42.2	...	..
Standard error	2.4	5.1	...	..	6.7	...	..
Sagittal							
Mean	32°	49°	55°	35	74°	59°	64
Standard deviation	24.9	25.9	...	..	33.5	...	..
Standard error	3.7	4.0	...	..	5.6	...	..
Horizontal							
Mean	25°	40°	40°	43	54°	39°	63
Standard deviation	16.3	29.7	...	..	31.5	...	..
Standard error	2.4	4.5	...	..	5.0	...	..

range of findings (shaded area) was indicated as twice the standard deviation on each side of the mean. In this correlation, the smallest discrepancies of mean results were found again between the two corrected lead systems. The range of findings was less in Frank's system than in the two conventional systems. Significant differences between different phases of QRS were found in the sagittal and horizontal planes. Marked changes in standard deviations occurred at the same time. This latter finding suggested contaminations by forces not belonging to a plane, e.g., contamination by sagittal forces in the frontal plane. This was investigated for the frontal plane by calculating $\frac{Z}{X}$ and $\frac{Z}{Y}$ ratios. A significant increase of these ratios was found toward the end of QRS, that is the possibility of contaminations by sagittal forces (Z) was greatest toward the end of QRS. This finding corresponded closely to the increase of the range of findings in the late portions of ventricular activation.

The variability of angular deviations from the reference system was determined by averaging the angular discrepancies for each subject and each system. (Table II.) This calculation indicates the mean change in angular deviation from the reference system during the QRS cycle *per subject*. This directional variability was found to be least for Frank's corrected system, larger for the tetrahedron and cube systems in increasing order.

If one assumes that the heart dipole equivalent is fixed in location for every subject, one must also assume that the direction of effective lead axes is fixed. If this is true, the range of angular variability per subject becomes limited and can be determined approximately by applying the rules of lead-vector projection [*6,13*]. Frank's model data on the strength, direction and contaminations of the conventional leads

were used for this procedure [*22,23*]. A hypothetical vector was rotated in steps of 30 degrees through each plane. The angular deviations from ideal, caused by the skewness of the conventional lead axes, were determined for each step. Consequently, the angular variability in this system was calculated in the same fashion as was done for the human subjects.

The angular variability found in man for conventional lead systems was compared to the maximal ranges of angular variability calculated from model data. A large percentage of the human series exceeded the maximums of the models. (Table II.)

When data of all correlations were compared between the series of normal subjects and the patients with heart disease, the means and standard deviations of Frank's system were found to be almost identical for the two groups. The ranges of angular deviations found in the pathologic series were somewhat larger using the two conventional lead systems. They increased maximally for the tetrahedron by a factor of 1.2 and for the cube of 1.3. Differences in results from normal subjects and patients with heart disease were not significant statistically.

COMMENT

Are the data obtained in artificial models valid to the same extent in living man? Relative lead strength correlations: The relative lead strength, as mentioned previously, is a function of absolute lead strength and direction. This correlation, therefore, is adequate for a comparison of lead characteristics in man and models. A close correlation between results predicted from experiments with models and actual findings in man was found in all six conventional leads tested. This is strong evidence that the electrocardiographic theory developed on the basis of experiments with torso models is correct. The discrepancies of conventional leads and ideal in models were almost the same as between characteristics of conventional leads and corrected leads in man. Therefore, it follows that the performance of corrected lead systems must approach ideal.

The ranges of findings for relative lead strength were considerably larger in man than those reported in models. This is partially explained by the method of calculation (amplitude ratios between compared and corrected systems). Depending on the polarity of the compared instantaneous vectors, the numerator or denominator of a ratio may be negative, leading to a negative result. The ranges of findings in Table I, therefore, extend to negative values. This has to be taken into account when the means and standard deviations of relative lead strength are compared. Even considering this point the ranges of findings appear to be large, and may be explained by the recent observations on the electrical conductivity of the human thorax. Schmitt [*24*] found relatively large differences of conductivity from one subject to another. Furthermore, the conductivity of the thorax changed markedly with deep inspiration or expiration.

Correlation of results obtained by the two corrected systems: The corrected systems of Schmitt and Frank exhibited the closest relationship in relative lead strength amongst the various systems tested. The study of angular deviations (Figs. 3 and 4) confirmed this observation. Frank's lead system deviated least in direction from the reference system. The close relationship found between the corrected lead systems differs strikingly from the marked discrepancies between the conventional systems tested in this study. Comparable differences between conventional lead systems have been reported by others previously [*5,22,25–28*]. As the design of Schmitt's and Frank's corrected systems differs considerably, the close relationship in performance can hardly be explained as being coincidental.

Frank [*8*] has stated that the accuracy of his leads depends critically on the correct horizontal level of chest electrode placement which should coincide with the level of the heart dipole equivalent. The fifth intercostal space, advocated by Frank [*8*] and used in this study, appears to be correct as a *mean* level. In individual cases, however, this level probably was too high or too low. Inaccuracies in the level of electrode placement exert their influence mainly on lead Z. Thus, it was found that the range of findings for angular deviations from the reference system was greatest in the two planes in which this lead is used (sagittal and horizontal). Contaminations by lead Z also appeared in the frontal plane. It might be argued that part of the discrepancies between the two corrected systems are due to inaccuracies of Schmitt's reference system. These discrepancies, however, agree closely with the predictions made by Frank [*8*] and with Schmitt's test results on Frank's lead system [*5*]. Therefore, it is safe to conclude that Schmitt's system was the more reliable of the

two corrected systems tested in this study. In spite of these drawbacks, Frank's system exceeded the accuracy of the two conventional systems markedly.

Are the characteristics of corrected leads the same in normal subjects and in patients with heart disease? No significant differences in relative lead strength results were found between the group of normal subjects and the patients with heart disease. The same was true when the two groups were compared for angular deviations. Differences in mean angular deviations did not exceed 8 degrees. Ranges of angular deviations were almost identical in normal subjects and patients with heart disease for Frank's system. They were somewhat larger in the pathologic group for the two conventional systems. It appears from the comparison of data obtained by the two corrected systems that no significant difference in performance exists between normal subjects and cardiac patients.

Is the use of corrected lead systems practical in routine application? No technical difficulties were encountered in the placement of electrodes for the two corrected lead systems. One electrode in Frank's system and two electrodes in Schmitt's system must be placed in the region of the breasts in female patients. This difficulty is identical with that found for leads V 3 and V 4 of the conventional electrocardiogram.

In Schmitt's system, five more electrodes are used than in the conventional electrocardiogram. No electrodes, however, need to be moved after the leads are applied to the patient. Using a resolver* an infinite number of scalar leads from any spatial direction desired or vectorcardiograms can then be recorded. In Frank's system two less electrodes are applied than for the electrocardiogram in clinical use at present. As pointed out previously, the performance of Frank's system was found to be less satisfactory than that of Schmitt. For this reason the use of more electrodes in Schmitt's leads appears justified because of the gain in accuracy.

Is the heart dipole equivalent fixed in location during the QRS cycle? As pointed out previously, any change in dipole position will change the direction and strength of effective lead axes. The lead corrections used in Schmitt's and Frank's lead systems provide constancy of lead direction and strength for a variety of dipole position changes in the heart region. Their accuracy therefore, will not be affected by dipole shifts during the QRS cycle. These shifts, however will change the characteristics of most conventional bipolar or unipolar leads. Corrections of conventional leads by changing their direction according to an average heart dipole position will have limited value when dipole shifts during QRS need to be taken into account. Therefore, it was important to attempt to resolve the question of movement versus fixation of the heart dipole equivalent during the QRS cycle.

From model data the maximal angular variability per subject was determined with the assumption of a fixed heart dipole. A large percentage of the subjects in this study exceeded this maximal calculated range. Although the calculated range is approximate only, this finding strongly suggests that dipole shifts have taken place during the QRS cycle. Another observation can serve as further support for this conclusion. The range of angular deviations from the reference system of Frank's corrected system was the same when the group of normal subjects and cardiac patients were compared. The two conventional systems, the tetrahedron and cube, showed an increase in range of 20 and 30 per cent, respectively in patients with heart disease. It is known that the pathway of activation of the ventricles is different from normal in many cardiac patients, especially in those with bundle branch block. A change of dipole position is more likely to occur in these patients than in normal subjects. Dipole shifts during QRS therefore, would explain the increase in the ranges of angular deviations. This range did not increase with Frank's system as the lead corrections make this system insensitive to dipole position changes. Scher [*29*] and Nelson and Hecht [*30,31*] arrived at similar conclusions recently using a different experimental approach.

Do unipolar precordial leads record preferentially from underlying portions of the heart? In experiments with torso models it was found that some of the conventional leads discriminate between different portions of the heart. A typical discrimination factor of 1:2 was observed [*4*]. This preferential recording, however, was not always in favor of portions of the heart underlying the electrode [*4,13*]. If such holds true in man, it appears extremely difficult to differentiate local and over-all features in a given precordial record. It cannot be concluded at

* A simple and inexpensive resolver was designed recently in this laboratory. It provides a selection of scalar electrocardiographic leads in steps of 15 degrees in three planes by switches.

present that unipolar precordial leads contribute additional diagnostic features not available from a corrected lead system. This problem awaits further study.*

CONCLUSIONS

The correlation of corrected and conventional lead systems in man resulted in two observations of interest. (1) The quantitative discrepancy between corrected and conventional leads in man was very similar to that reported in models between conventional leads and ideal. (2) Two corrected lead systems, different in lead design, showed a very close relationship in their performance in man.

As this finding was predicted on the basis of recently developed electrocardiographic theory, the conclusion can be drawn that this theory applies to man. Recognition of the validity of the new electrocardiographic concepts implies several other criticisms of bipolar and unipolar leads which are in clinical use at present: (1) The direction of effective lead axes cannot be predicted from the anatomic site of electrode placement. (2) The direction and strength of conventional leads depend critically upon the position of the heart dipole equivalent in relation to the thorax. This position differs from one subject to another and from one instant to another in the same subject. (3) Conventional leads are not suitable for vectorcardiography because of their instability in lead strength and direction. The same applies to the plotting of vectors from conventional leads. Furthermore, almost all conventional leads are subject to variable contaminations by forces from undesired directions. (4) Conventional leads cannot be "corrected" by changing lead direction and amplification factors, since these leads will still be sensitive to heart dipole variations.

The use of corrected electrocardiographic leads offers many advantages which appear to have more than academic merits. (1) Lead direction and strength are constant regardless of heart dipole position variations. This facilitates a more quantitative approach to electrocardiographic interpretations. (2) The wide range of findings in normal subjects encountered in clinical electrocardiography becomes considerably smaller when corrected leads are used [*32*]. It can be expected that the large overlap between normal and pathologic findings will decrease and that pathologic findings then will have more significance. (3) Corrected leads can be used for the recording of both scalar electrocardiograms and vectorcardiograms. An infinite choice of scalar leads can be recorded by means of a resolver without the necessity of moving electrodes. Scalar electrocardiograms and vectorcardiograms become interchangeable in all planes. This is not possible with conventional lead systems. (4) As all electrical information possibly available from the heart seems to be contained in three basic orthogonal leads, the number of leads taken for clinical purposes can be reduced considerably.

On the basis of the present findings it appears that the clinical use of corrected electrocardiographic lead systems will lead to greater accuracy and reliability in the diagnosis of heart disease.

SUMMARY

The accuracy of several corrected electrocardiographic lead systems that were developed on the basis of experiments with torso models was tested in man. Two corrected, orthogonal lead systems (Schmitt's SVEC III and Frank's) and two lead systems that use conventional bipolar and unipolar leads (Wilson's tetrahedron and Grishman's cube) were applied to forty normal subjects and fifteen patients with heart disease. Schmitt's system, the most reliable in model studies, was used as the reference. Relative lead strength and angular deviations of instantaneous vectors in different phases of the QRS cycle were studied. The findings in man were compared with those obtained from torso model studies. Actual and predicted results were closely related. It was concluded that the electrocardiographic theory developed on the basis of torso model studies applies to man, and that the corrected lead systems are more accurate in man than conventional bipolar or unipolar leads. Schmitt's system was more reliable than the simpler system of Frank. Discrepancies between corrected systems, however, appeared very small when compared to the inconstancy of conventional lead performance. No technical difficulties were encountered in the application of the corrected leads. In a large number of cases, the angular variability of conventional leads exceeded the maximal ranges calculated for a fixed dipole position. This finding suggests

* A controlled (double-blind) study on a large series of abnormal electrocardiograms, using conventional precordial leads and resolved corrected leads from comparable directions is in progress now in this laboratory.

strongly that dipole shifts take place during the QRS cycle.

From the findings of the present study, it appears that the accuracy of clinical electrocardiography can be greatly enhanced by the application of corrected lead systems.

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ADDENDUM

Since the preparation of the manuscript a correlation of four orthogonal lead systems has been reported by Langner, P. H., Okada, R. H., Moore, S. R. and Fies, H. L. (*Circulation*, 17: 46, 1958). These authors also found a very close relationship in the performance of Schmitt's and Frank's lead systems.

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Coronary Embolism*

Review of the Literature and Presentation of Fifteen Cases

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SINCE the original description of coronary artery embolism in 1856 by Virchow [*1,2*] sixty-two well documented cases have appeared in the literature, usually as isolated case reports.

In the discussion of coronary artery embolism, the standard cardiology and pathology texts [*3–8*], as well as reports in the literature [*9–26*], place emphasis on the rarity of its occurrence. The statistical incidence has been variously noted in several series. In 1,750 consecutive autopsy cases reported by Benson and Hunter [*27*], fourteen deaths in 200 cases of coronary artery obstruction were attributed to coronary artery embolism. Kirschbaum [*28*] selected reports of 612 cases of severe coronary artery disease from 6,754 consecutive necropsies; of fifty-seven cases in which coronary artery occlusion was the direct cause of death, only four deaths were due to coronary artery embolism. In another series [*29*] of 762 cases of coronary disease selected from reports of 2,877 postmortem examinations, six cases of coronary artery embolism were described. Wolff and White [*30*] reported twenty-three cases of coronary artery occlusion, which came to autopsy; death in four of these cases was due to embolism. Parkinson and Bedford [*24*] reviewed eighty-three autopsy reports of cases of cardiac infarction; in four death was due to coronary artery embolism. In only two cases in this series were the patients under thirty years of age, and coronary artery embolism was found in both.

In a study [*31*] of 442 clinical cases of subacute bacterial endocarditis, autopsy was performed in eighty-nine, in twelve cases (13 per cent) there was a coronary artery embolism, in ten of these myocardial infarction was also present. Saphir, Katz and Gore [*32*] studied reports of seventy-six fatal cases of subacute bacterial endocarditis. They found seventeen cases of coronary artery embolism among the thirty-six cases in which myocardial infarction was present.

In the years 1929 through 1957 there have been, at the Mount Sinai Hospital, eleven well documented cases of coronary artery embolism which were confirmed by postmortem examination,† representing an incidence of 0.06 per cent in 17,469 consecutive autopsy cases. In addition, during the six month period January through June 1957 three unsuspected cases of coronary artery embolism, incidental to the cause of death, have been found at postmortem examination. It is our purpose to report these fourteen cases (Tables I and II) and one other case which was recently brought to our attention.‡ The following interesting cases are presented in greater detail.

CASE REPORTS

CASE I. M. W. (P. M. 17046). This was the first admission to the Mount Sinai Hospital for this fifty-nine year old white woman who had a history of weakness of four months' duration. During this period she had had an unexplained loss in weight and anemia, with several showers of petechiae. She was admitted to the hospital for diagnostic evaluation. Examination of the heart revealed a grade 3 systolic murmur at the apex. Blood cultures were positive for Streptococcus viridans. Intensive antibiotic therapy for subacute bacterial endocarditis was instituted. On the eleventh hospital day pulmonary edema and shock developed suddenly, and an electrocardiogram revealed an acute anterolateral myocardial infarction. Despite supportive measures she died several hours later. Postmortem examination revealed subacute bacterial endocarditis of the mitral valve (Fig. 1), moderately sclerotic coronary arteries, an embolus in

† One case previously reported by Zak and Elias [*68*].

‡ Information kindly supplied by Dr. Isadore E. Gerber.

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TABLE I

CORONARY ARTERY EMBOLISM

THE MOUNT SINAI HOSPITAL, 1929–1957

Autopsy No.	Year	Age (yr.)	Sex	Underlying Disease	Coronary Arterial Site of Embolus	Type of Death	Status of Coronary Arteries	Status of Myocardium
6650	1929	43	Male	Acute bacterial endocarditis	Left main	Sudden	Negative	Negative
7482	1930	36	Male	Subacute bacterial endocarditis	Left main	Delayed (4 days)	Negative	Posterior wall infarct
7667	1931	30	Male	Subacute bacterial endocarditis	Left anterior descending	Not related to cause of death	Negative	Negative
8475	1932	28	Female	Acute bacterial endocarditis	Left anterior descending	Delayed (8 days)	Negative	Negative
9631	1935	25	Male	Subacute bacterial endocarditis	Left coronary (two emboli)	Sudden	Negative	Posterior wall infarct
89*	1939	24	Female	Subacute bacterial endocarditis	Left main extending to left anterior descending	Sudden	Negative	Negative
11937	1941	68	Male	Pulmonary vein thrombosis associated with carcinoma of pancreas	Right main	Not related to cause of death	Moderate sclerosis	Subacute posterior wall infarct
12298	1942	45	Male	Ball valve thrombus of left atrium (mitral stenosis)	Right main	Not related to cause of death	Negative	Subacute posterior wall infarct
13563[48]	1946	35	Male	Thrombus in proximal portion of right coronary	Right ("several emboli")	Sudden	Marked sclerosis	Acute and subacute posterior wall infarcts
14730	1946	77	Female	Acute bacterial endocarditis	Left anterior descending	Sudden (8 days after clinical infarction)	Sclerotic	Subacute anteroseptal infarct with rupture
16447	1954	35	Female	Monilial thrombosis of left atrial appendage	Left anterior descending, left main and right main	Acute (1 day)	Negative	Scattered septal and anterior wall infarcts
17046	1956	59	Female	Subacute bacterial endocarditis	Left circumflex	Acute (1 day)	Moderate sclerosis	Posterior wall infarct

* Postmortem examination performed at the Hudson County Tuberculosis Hospital and Sanitorium.

TABLE II

CORONARY ARTERY EMBOLISM INCIDENTAL TO CAUSE OF DEATH

THE MOUNT SINAI HOSPITAL, JANUARY THROUGH JUNE 1957

Autopsy No.	Year	Age (yr.)	Sex	Underlying Disease	Site of Embolus	Nature of Embolus	Status of Coronary Arteries	Status of Myocardium
17290	1957	12	Female	Rheumatic heart disease with calcified left atrial mural thrombus	Left main and right main	Calcium	Negative	Negative
17311	1957	52	Female	Rheumatic heart disease with calcified left atrial mural thrombus	Right main	Calcium	Moderate sclerosis	Negative
17466	1957	72	Male	Terminal endocardiosis (aortic) secondary to bronchogenic carcinoma	Left anterior descending	Non-bacterial vegetation	Slight sclerosis	Old fibrosis

the left circumflex artery (Fig. 2) and an acute posterolateral wall myocardial infarction.

CASE II. M. S. (P. M. 16447). This was the fourth admission to the Mount Sinai Hospital for this thirty-four year old white woman who in January, 1954, had been found to have pancytopenia. Hematologic study at this time revealed an aplastic bone marrow, and she was treated with cortisone and blood transfusions. In November, 1954, she underwent splenectomy in an effort to improve the pancytopenia. She was subsequently treated with tetracycline and blood transfusions until March, 1955, when she entered the Mount Sinai Hospital with signs and symptoms of hepatitis. Physical examination revealed a diffuse grade 1 precordial systolic murmur, hepatomegaly and slight icterus. From the time of admission a spiking fever with temperatures up to 105°F. persisted. Blood cultures were positive for Staphylococcus aureus on only one occasion; the patient was treated with appropriate antibiotics. On the nineteenth hospital day a pericardial friction rub was heard, and on the twentieth hospital day she complained of precordial and left shoulder pain. Following this tachypnea, tachycardia and a loud apical systolic murmur developed. Death occurred on the twenty-first hospital day. Postmortem examination revealed a thrombus of the left atrial appendage, and emboli in the left

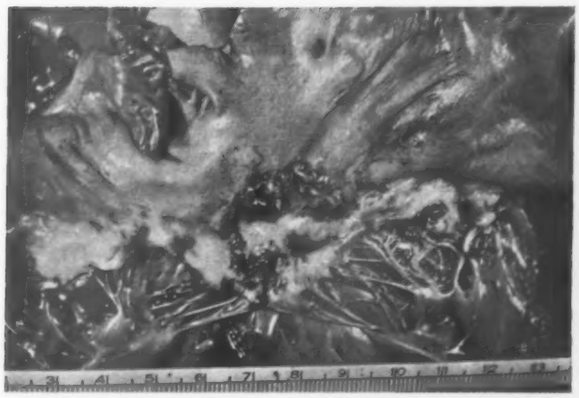

FIG. 1. Case I. Subacute bacterial endocarditis of the mitral valve in a normal heart.

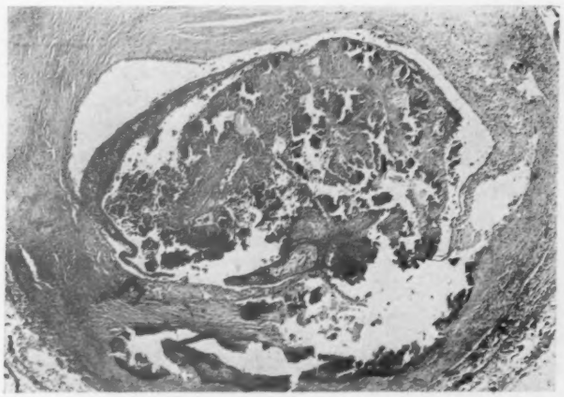

FIG. 2. Same case. Coronary artery embolus composed of vegetative material.

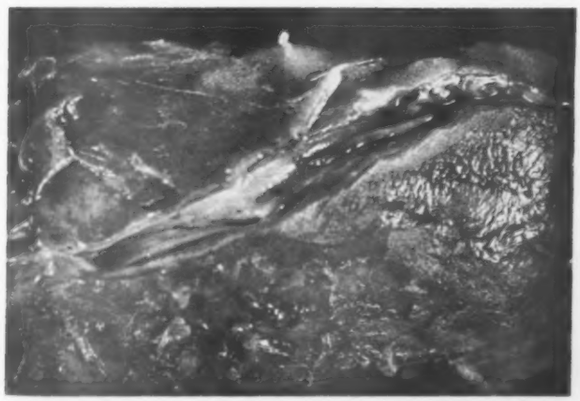

FIG. 3. Case II. Coronary artery embolus.

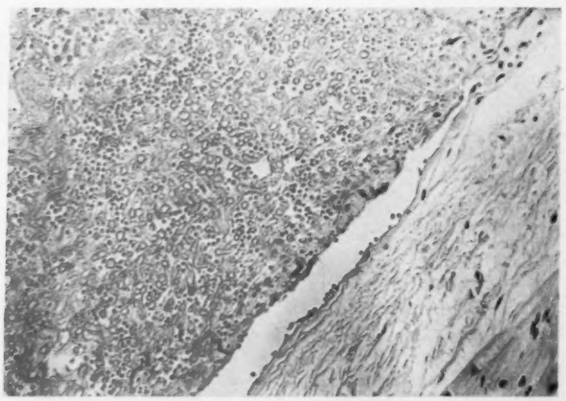

FIG. 4. Same case. Thrombus of left atrial appendage composed of Candida albicans.

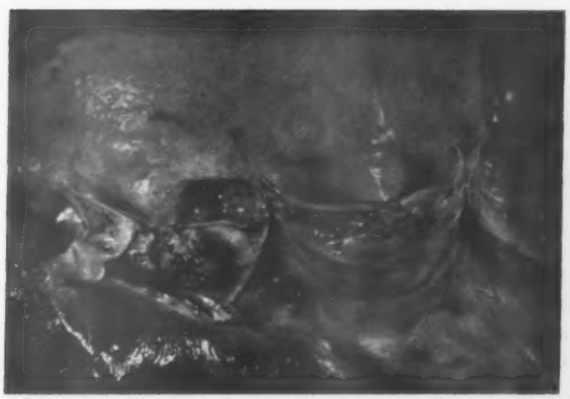

FIG. 5. Case III. Terminal endocardiosis of the aortic valve.

FIG. 6. Same case. Coronary artery embolus.

anterior descending, left circumflex and right main coronary arteries. (Fig. 3.) These thrombotic and embolic masses were composed of fibrin and masses of Candida albicans. (Fig. 4.) There were scattered small fresh infarcts of the anterior myocardial wall, but the coronary arteries *per se* showed no intimal involvement. In addition there was evidence of monilial involvement of the pericardium, pharynx, cecum, liver and lungs. Culture of the lungs yielded Cryptococcus neoformans in addition to Candida albicans.

CASE III. S. F. (P. M. 17466). This was the second admission to the Mount Sinai Hospital for this seventy-two year old white man who had a history of recurrent

cerebral accidents manifested by focal neurologic signs during the eighteen months prior to admission. Physical examination on admission revealed, in addition to aphasia and a left hemiparesis, marked cervical adenopathy. Roentgenographic examination of the chest disclosed a mass in the left hilar region and areas of bronchopneumonia. Shortly after admission he became markedly lethargic; he died on the fifteenth hospital day. Postmortem examination revealed a bronchogenic carcinoma and a terminal endocardiosis. (Fig. 5.) A bland embolus which measured 1 by 2 mm. was lodged in the left anterior descending coronary artery (Fig. 6), and there were multiple anemic infarcts of the spleen. The coronary arteries showed slight sclerosis; the myocardium appeared normal. The brain showed multiple arteriosclerotic vascular lesions.

TABLE III
FREQUENCY OF UNDERLYING DISEASE

Underlying Disease	No. of Patients	Per cent of Total
Subacute bacterial endocarditis	39	52.7
Acute bacterial endocarditis	8	10.9
Intra-cardiac thrombus	8	10.9
Luetic aortitis	4	5.4
Aortic atherosclerosis	3	4.1
Thrombus (paradoxical)	3	4.1
Aortic thrombus (? etiology)	2	2.7
Proximal coronary artery thrombus	2	2.7
Pulmonary vein thrombus	1	1.3
Tuberculous material via pulmonary vein	1	1.3
Tumor (paradoxical)	1	1.3
Calcific valve	1	1.3
Not stated	1	1.3
Total	74	100.0

COMMENTS

Although many explanations have been advanced to explain the rarity of embolization to the coronary arteries [*10,16,18,22,23,25,33–35*], there has been no completely satisfactory elucidation of the problem. The comparatively small coronary artery caliber in relation to that of the aorta, coupled with the rapid aortic linear flow and the right-angle origin of the coronary arteries from the aorta, makes the lodging of a free embolus in the coronary arteries less likely than the propulsion of this embolus peripherally with the main aortic stream. Emboli larger in caliber than the coronary artery orifices similarly will be driven peripherally. Also, the preponderance of coronary artery perfusion is assumed to occur during diastole, after the greatest volume of the left ventricular ejection has passed the coronary orifices. Furthermore, during systole, when the major aortic flow occurs, the coronary orifices are assumed to be at least partially covered by the aortic valve cusps, thus affording protection against the entry of an embolus.

Tabulation of the causes of coronary artery embolism includes [*7,8,12,16,21,25,36–42*]: bacterial or bland valvular and mural endocardial vegetations; syphilitic or atherosclerotic aortic lesions; intracardiac mural thrombi; atheromatous material or thrombi in coronary arteries; atheromatous material, thrombi, tumor or infectious material from the pulmonary veins; thrombi or tumor in the peripheral veins by paradoxical embolization; calcific valvular material; and air or fat emboli.

Analysis of the underlying diseases associated with coronary artery embolism shows subacute bacterial endocarditis to be the most frequent single cause [*24,25,34,43–47*]. Porter and Vaughan [*41*] and Shrader et al. [*42*] have reported the incidence of subacute bacterial endocarditis as the basic disease in coronary artery embolism to be 40 and 42 per cent, respectively. Cheng and co-workers [*36*], Cordeiro and Coelho [*16*] and Hamman [*37*] all report an incidence of about 50 per cent. Brunson [*13*] reports 80 per cent of cases of coronary artery embolism associated with subacute bacterial endocarditis, but this includes cases of multiple small emboli. In agreement with previous reports, subacute bacterial endocarditis was the most common underlying disease in this series, occurring in thirty-nine of seventy-four cases (52.7 per cent). (Table III.) Among our cases is the first reported instance of fungal embolism (Case II). We have also reported (Table II) three instances of coronary artery embolism incidental to the cause of death, observed at the Mount Sinai Hospital during a recent six month period. Two of these were secondary to calcified atrial thrombi and one to terminal endocardiosis. This represents an incidence of 1.5 per cent, suggesting that nonfatal coronary artery emboli may not be a rare entity.

The consensus in the literature [*15,18,40,45,48–53*] is that embolic occlusion of the left coronary artery, and especially of the left anterior descending artery, is more frequent than that of the right coronary artery. In their reviews

of the literature Porter and Vaughan [*41*], Ramos et al. [*34*] and Shrader and co-workers [*42*] report embolic occlusion of the left coronary artery in 77, 79 and 84 per cent, respectively. Ramos, LeVoci and Fonseca [*34*] and Padilla and Cossio [*54*] offer as explanation the fact that the caliber of the left coronary artery is greater than that of the right; in receiving more of the blood flow it concomitantly may receive more of the emboli. Schlesinger and Zoll [*55*] state that the difference in the pattern of coronary artery branching may explain the different incidence of occlusions in the left and right coronary arteries; the right-angle exit of the left coronary artery branches as they enter the myocardium makes them more liable to embolic occlusion than the acute angle branching pattern of the right coronary artery.

That the more frequent occurrence of left coronary artery emboli may be factitious is suggested by Gallavardin and Dufourt [*56*] who cite results of experimental coronary artery ligation in the dog, showing that left-sided ligation causes sudden death in 50 to 80 per cent, whereas right-sided ligation is fatal in only 15 per cent; therefore, the comparative incidence of right and left coronary artery emboli may not differ, the left preponderance being explained by its propensity to fatality and subsequent detection at postmortem examination.

In considering the preponderance of fatal left coronary artery embolic occlusion, it is interesting to speculate on the effect of the early bifurcation of the left main coronary artery and the rapid decrease in caliber distal to the bifurcation. These two factors may predispose to the more proximal lodging of an embolus in the left coronary artery, thus occluding the blood flow to a larger muscle mass, whereas a similar embolus in the right coronary artery would be carried more distally, the resultant occlusion affecting a lesser muscle mass.

Left coronary artery embolism accounted for 75 per cent of the reported cases (Table IV) with an almost equal incidence in the left anterior descending and left main coronary arteries, there being 30 and 26 instances, respectively.

Clinical Manifestations. Coronary artery embolization presents as an acute cardiovascular episode characterized by varied combinations of pain, shock, arrhythmia and pulmonary edema. It must be a significant etiologic consideration in the differential diagnosis of sudden death in a young adult. Review of the literature and of the cases in our series reveals that two-thirds of the patients with bacterial endocarditis as the underlying disease died suddenly as a result of the coronary embolism; one-third of the patients in whom death was due to coronary embolism in this group followed a more protracted clinical course, presenting with an acute myocardial infarction. Among the patients with an etiology other than bacterial endocarditis, all the deaths from coronary embolism occurred suddenly. This sudden death may be related to the nature of the embolic material, to the nature of the underlying disease, to the general condition of the patient or to the fact that in patients dying later in the course of their disease the diagnosis was incorrect as they were considered to have had a coronary thrombosis without a search being made for emboli.

TABLE IV
SITE OF EMBOLUS

Site of Embolus	No. of Patients	Per cent of Total
Left anterior descending	26	35.1
Left main	24	32.4
Right main	9	12.2
Left and right	4	5.4
Left circumflex	3	4.1
Two left	2	2.7
Right (several emboli)	1	1.3
Not stated	5	6.8
Total	74	100.0

RELATIONSHIP OF UNDERLYING DISEASE TO TYPE OF DEATH*

Type of Death	Patients with Bacterial Endocarditis	Patients without Bacterial Endocarditis
Sudden	25	24
Delayed	13	0

* In twelve cases insufficient information was furnished or the coronary embolism was not the cause of death.

"Males between 25 and 35 without clinical evidence of cardiac disease, in whom death occurred suddenly" [*8*] typifies the clinical picture of bland coronary artery embolism. That coronary artery embolism is primarily a disease of the younger age group is also empha-

sized by Ramos et al. [*34*] and by Thorel [*52*]. Shrader and co-workers [*42*] in their review of the literature found most cases occurring before age forty, with about 75 per cent incidence in males. Sudden death [*37,40,48*] is usually attributed to the lack of an adequate collateral circulation in the young patient with normal coronary arteries [*50,57*], although no definite evidence of slower death has been found in the older age group [*42*].

TABLE V
TYPE OF DEATH

Type of Death*	No. of Patients	Per cent of Total
Sudden	42	60.0
Delayed	16	22.9
Acute†	6	8.5
Not related	4	5.7
Not stated	2	2.9
Total	70	100.0

* Four patients (5.4 per cent) are living; the diagnosis was made clinically and by electrocardiogram.
† Less than twenty-four hours' duration.

Our statistics as regards the type of death (Table v) are in agreement with those previously reported, sudden death accounting for 60 per cent of the fatalities. We were unable to correlate the rapidity of occurrence of death with the age of the patient and the associated status of the coronary arteries. However, the rapidity of death differed markedly with occlusion of the right and left coronary arteries, acute death occurring in forty-three of fifty-three cases of left coronary artery embolization and in three of seven cases of right coronary artery embolization. Although too small a series for valid comparison the observation suggests the lesser gravity of right coronary artery embolization, as previously implied by Libman and Friedberg [*94*].

Fifty of seventy-one patients were under age forty, with all but five under sixty years of age. (Table VI.) In agreement with previous reviews, there was a preponderance of males affected, 66.2 per cent. (Table VII.)

The requisite criteria for the diagnosis of coronary embolism as the cause of death in our series included the presence of an occluding mass in a major branch of the coronary artery, identification of the site of origin of the embolus, and the demonstration of an essentially normal arterial intima at the area of occlusion. The sixty-two case reports in the literature used for our evaluation [*1,2,15,16,18,19,21,30,33–36,38–41,45,48–51,53,56,57,61,69–93*] fulfilled these criteria; insufficient specific information was furnished in several other case presentations [*11,17,20,27,33–35,52,58–67*], although the clinical picture described was compatible with coronary embolization.

TABLE VI
AGE

Age (yr.)	No. of Patients	Per cent of Total
11–20	5	6.8
21–30	19	25.7
31–40	26	35.1
41–50	14	18.9
51–60	2	2.7
61–70	4	5.4
71–80	1	1.3
Not stated	3	4.1
Total	74	100.0

TABLE VII
SEX

Sex	No. of Patients	Per cent of Total
Male	49	66.2
Female	23	31.1
Not stated	2	2.7
Total	74	100.0

SUMMARY

1. Fifteen cases of coronary artery embolism confirmed at post-mortem examination are presented.

2. The literature regarding coronary artery embolism is reviewed and the clinical manifestations discussed.

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ADDENDUM

Since the preparation of the manuscript, several additional reports of cases of coronary

embolism have appeared. Among these were four cases [*95–98*] in which the embolus was the cause of death or possibly related to the cause of death. There have been four reports of post-mortem studies [*99–102*], which enumerated six instances of coronary embolism incidental to the cause of death. Four of these emboli were calcareous in nature and two presumably followed aortic valvulotomy [*99,100*].

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The Pathogenesis and Treatment of Hyponatremia in Congestive Heart Failure*

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In recent years there has been increasing awareness of the multiplicity of factors contributing to the development of edema in congestive heart failure. The studies of Proger, Ginsberg and Magendantz [*1*] and of Schroeder [*2*] firmly re-established earlier suggestions that the basis for fluid accumulation in edematous patients is retention of sodium, secondary to which water is retained to preserve the isotonicity of the body fluids. Although there has been considerable controversy during the past decade concerning the initiating mechanisms, the primary role of sodium retention in the pathogenesis of cardiac edema has been generally accepted because of the therapeutic success of the low sodium diet and of measures for promoting sodium excretion, and the apparent ability of most cardiac patients to excrete even the large amounts of fluid given on the Schemm regimen [*3*], when maintained on a restricted sodium intake.

However, metabolic studies from several laboratories [*4*] have revealed that not infrequently the weight gained or lost by cardiac patients during the development or mobilization of edema is greater than can be explained in terms of sodium balance alone. These observations and reports that the urine of edematous cardiac patients may contain increased quantities of antidiuretic material [*5*] have led to a re-investigation of the older notion that, in certain phases of congestive failure, there may be retention of water in excess of sodium.

The present communication is concerned with the development of such primary water retention in a series of cardiac patients, under study in a metabolic ward, in whom chronic congestive failure was acutely intensified either by escape from digitalization, the development of digitalis toxicity, or a severe, acute respiratory infection. The data, which have previously been reported in preliminary form [*6*], suggest that an antidiuretic mechanism is invoked, which results in retention of water in excess of sodium, leading to increasing edema and hyponatremia without external loss of sodium. This sequence, which has been observed in many other patients following similar clinical conditions, has also been reproduced by administration of pitressin® tannate in oil [*7*].

MATERIAL AND METHODS

The patients, who were in congestive failure as a consequence of chronic rheumatic heart disease, were maintained on a metabolic ward on a low sodium diet (12 to 15 mEq.), with digitalis and bedrest. Two isocaloric diets, containing equivalent amounts of sodium, chloride, potassium, nitrogen, phosphorus and water, were given on alternate days to diminish the monotony of the metabolic regimen. Intakes, calculated in the usual manner, were based on repeated analyses of the diets.

The patients were weighed each morning on a beam balance, accurate to approximately 10 gm. Stools, which were pooled for three- to six-day periods, and daily urines were refrigerated until analyzed. At the beginning of each stool collection period, or more frequently if indicated, venous blood was withdrawn without stasis, and venous pressure and circulation times (decholin® and ether) were determined. Daily urinary excretion of creatinine, daily urinary and pooled fecal excretions of sodium, chloride, potassium, phosphorus and nitrogen were measured. The corresponding serum concentrations, the serum total protein, albumin, globulin, uric acid and bicarbonate

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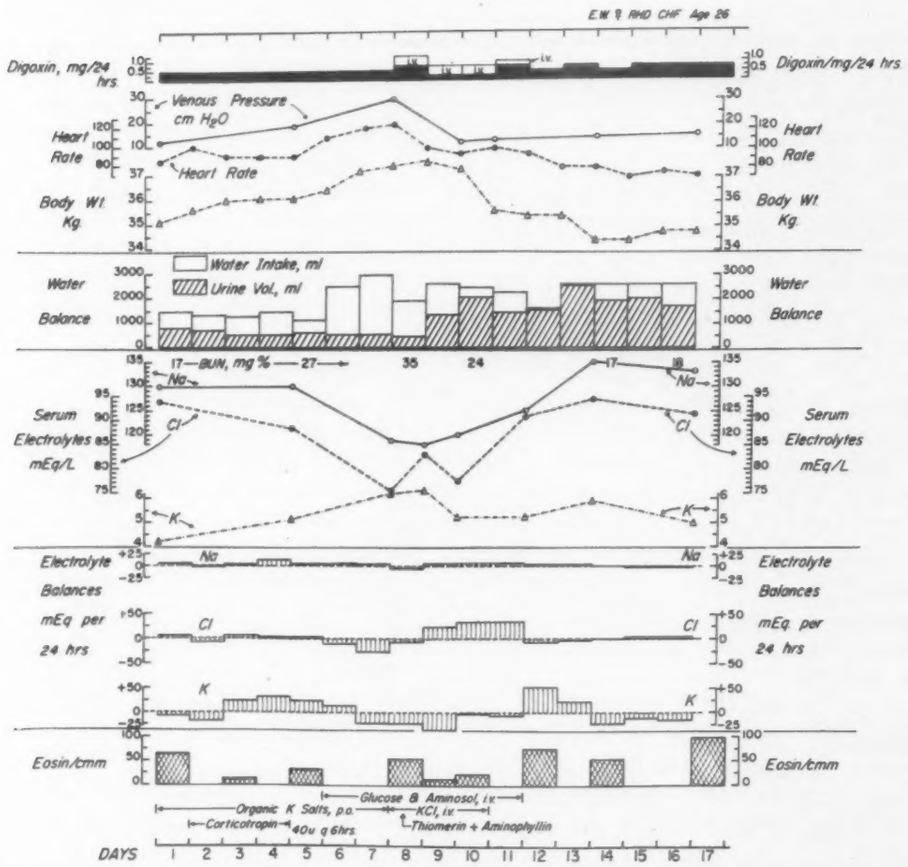

FIG. 1. Water retention following insidious escape from digitalization in a patient (E. W.) on low sodium intake.

concentrations, hematocrits, and circulating blood eosinophil counts also were determined.

Blood, urine and ashed samples of diets, stool or vomitus were analyzed by methods described previously [*8*]. Metabolic balances were estimated on the basis of these analyses.

From the chloride balances and serum chloride concentrations, changes in extracellular fluid volume were calculated in the usual manner. The initial chloride space was assumed to be 20 per cent of the patient's dry weight, plus the estimated volume of edema fluid. All electrolyte concentrations were corrected for the Donnan equilibrium and for serum water content, estimated from the serum total protein concentration. From the serum sodium and potassium concentrations, the corresponding metabolic balances and the calculated extracellular fluid volume, changes in extracellular and intracellular sodium and potassium distribution were calculated. Correction of the potassium balances for changes in nitrogen balance was made after calculation of the effect of changes in non-protein nitrogen on external nitrogen balance. Cumulative balances for chloride and sodium were also adjusted by subtracting the daily extrarenal, extrafecal loss, estimated from the daily balances during a period of stable weight and serum electrolyte concentrations [*9*].

RESULTS

Escape from Digitalization. Figure 1 presents pertinent data on patient E. W., a twenty-six year old woman with rheumatic heart disease, mitral stenosis and insufficiency, in chronic congestive failure.* This patient had entered the hospital seven weeks previously in severe congestive failure. On bedrest, low sodium intake,

* In Figures 1, 2, 3 and 4, the significant data are presented graphically from the top down, in the following order: (1) daily dose of digoxin; (2) venous pressure; (3) apical (cardiac) rate; (4) body weight; (5) water balance, daily urine volume (crosshatched boxes) being superimposed on the fluid intake (open boxes) which is plotted upwards from the zero or baseline; (6) serum electrolyte concentrations; (7) daily balances for sodium, chloride and potassium, positive balances being plotted above, and negative balances below the baseline; (8) circulating eosinophil counts; and (9) other medications.

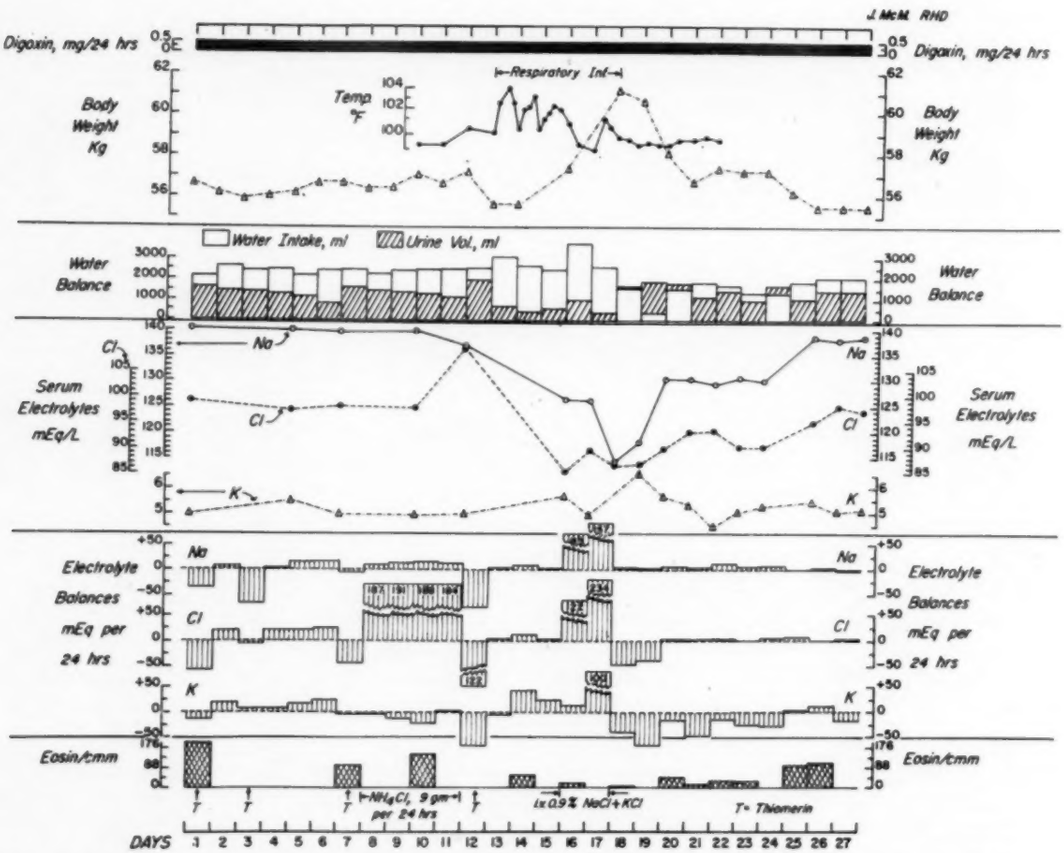

FIG. 2. Water retention and hyponatremia, following intensification of congestive heart failure during a severe febrile respiratory infection in a cardiac patient (J. M.).

maintenance dose of 0.25 mg. of digoxin administered twice daily, and periodic administration of ammonium chloride, mercurial diuretics and cation exchange resins [*8*] most of the edema disappeared. However, for a week prior to day 1 (see Fig. 1), she had manifested increasing signs of congestive failure, with a low grade fever, fall in serum sodium to 130 mEq./L. and diminished urine volumes.

Because of the daily fever, increasing anorexia and mild hyponatremia, she was given a three-day therapeutic trial of corticotropin (40 units administered intramuscularly every six hours) without significant improvement, and by day 5 her blood urea nitrogen had risen to 27 mg. per cent. From days 6 through 11, because of the poor oral intake and the possibility that the oliguria reflected simple dehydration, she was given daily intravenous infusions of 500 to 1,000 ml. of 5 per cent aminosol® in 5 per cent dextrose in water, and on days 8, 9 and 10 an additional 500 to 1,000 ml. of 5 per cent dextrose in water, containing approximately 40 mEq. of potassium chloride. Despite the increased fluid intake, the urine volume remained low and the blood urea nitrogen continued to rise. Throughout the period of study the sodium balance could have been only slightly positive at most because the low sodium intake was maintained. As the body weight increased, due to retention of water without sodium, tachycardia and dyspnea increased and the serum sodium concentration was diluted to 119 mEq./L. by day 8. At this time, when the patient was given an intravenous injection of mercaptomerin followed two hours later by aminophyllin, a diuretic procedure generally effective even in mercurial resistant patients [*10*], no diuretic response was noted.

On day 8 a total of 1.25 mg. of digoxin was given intravenously and orally and on day 9 0.75 mg. The apical cardiac rate began to fall and, with better digitalization, the urine volume rose, body weight decreased, the serum sodium concentration increased slightly, and the venous pressure dropped from 30 to 12 cm. H_2O. On

day 10 the heart rate remained in the 80's, the urine volume increased again, without loss of sodium, and the body weight fell an additional 1.7 kg. Subsequently, by virtually titrating the patient's digitalis requirement by frequent checking of the apical rate and rhythm, the heart rate was maintained between 70 and 80 per minute. The increase in urine volume without loss of sodium persisted, and by day 14 the body weight was below, and the serum sodium concentration above the corresponding levels on the first day charted.

Comment: It would appear that in this case escape from digitalization had invoked an antidiuretic mechanism, leading to the retention of water in excess of sodium, with increasing edema and the development of hyponatremia without external loss of sodium. The usual calculations of fluid and electrolyte distribution, based on changes in serum electrolyte concentrations and metabolic balances, revealed no significant transfers of sodium between the major body fluid compartments. The fall in serum sodium and chloride concentration therefore represents dilution of the body fluids by retained water.

At the height of this antidiuretic response, other mechanisms promoting salt and water retention, which are invoked whenever the cardiac output becomes inadequate for the body's metabolic needs, probably also were activated. This explains the complete absence of diuretic response following the administration of mercaptomerin and aminophyllin [*10*]. However, once adequate digitalization had augmented the cardiac output the antidiuretic mechanism was inhibited, with consequent diuresis of water without loss of sodium. In this patient with a regular sinus rhythm, the progressive decrease in cardiac rate to normal, which preceded the water diuresis, probably reflects the increase in cardiac output due to improved myocardial function.

Severe Respiratory Infection. Figure 2 illustrates the development of a similar acute antidiuretic reaction in a thirty-one year old man with chronic congestive failure secondary to rheumatic heart disease, in whom the increased disproportion between cardiac output and body metabolic needs followed the onset of a severe respiratory infection. Prior to the period illustrated on the chart, his serum sodium level had remained at 140 mEq./L., despite rigidly restricted sodium intake and repeated injections of mercurial diuretics. As anticipated, each succeeding mercurial injection produced progressively less diuresis, until on day 7 administration of mercaptomerin produced chloriuresis and kaliuresis with minimal natriuresis [*10*]. On this account 9 gm. of ammonium chloride was given daily for four days before the next injection of mercaptomerin, which resulted in moderate natriuresis and somewhat greater chloriuresis.

On this day a slight rise in temperature was noted (cf. temperature curve above body weight, Fig. 2), the first sign of a severe pneumonitis. The next day his temperature spiked to 104°F. and, despite maintenance of adequate fluid intake, the urine volume fell sharply, the body weight increased due to retention of water, and characteristic dilution hyponatremia and hypochloremia developed. On days 16 and 17, in order to determine whether this acute antidiuretic reaction was a response to the contraction of extracellular fluid volume after the repeated mercurial diureses, intravenous infusions of isotonic sodium chloride, containing potassium chloride, in amounts more than sufficient to replace electrolyte lost during the previous diureses, were given. Nevertheless, the oliguria persisted, the weight continued to rise, and the serum sodium fell further to 114 mEq./L.

However, the pneumonitis responded to antibiotic therapy, and the fever gradually subsided. After day 18, the temperature remained normal, the urinary water excretion increased, the body weight fell, and the serum sodium rose. On day 19, despite restricted fluid intake, the urine volume remained high, again without loss of sodium, the body weight fell 1.5 kg., and the serum sodium rose to 130 mEq./L. Subsequently, water diuresis continued and control body weight and serum electrolyte concentrations were gradually achieved. During the stress of intensification of congestive failure as the result of the infection in this patient with a fixed, low cardiac output, the circulating eosinophils virtually disappeared, with subsequent return to normal upon his recovery.

With the onset of diuresis the increased urinary excretion of potassium and nitrogen brought the corresponding elevated serum concentrations to more normal levels, as in the case of patient E. W. (Fig. 1.) The possible significance of this fall in serum potassium with improved cardiovascular status will be discussed subsequently.

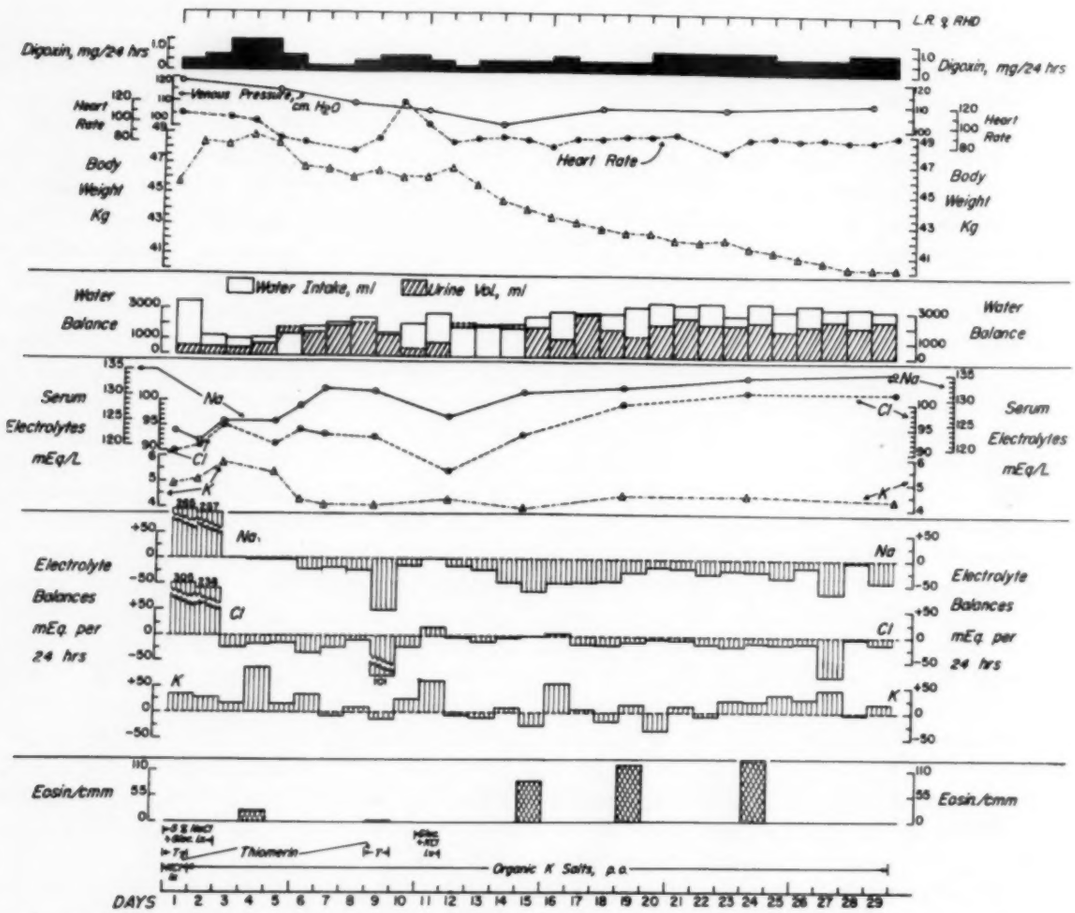

FIG. 3. Oliguria and hyponatremia in a patient (L. R.) in severe congestive failure with electrocardiographic changes suggestive of overdigitalization, but due to myocardial potassium depletion.

Comment: It should be emphasized that this patient was adequately digitalized throughout the study and that the disproportion between cardiac output and body metabolic needs was a consequence of the increased metabolic demands resulting from illness and elevated temperatures. Moreover, the water retention was shown not to have resulted simply from previous contraction of the extracellular fluids, since it responded promptly to control of the infection by antibiotics.

Increased Digitalis Sensitivity Due to Potassium Depletion. Figure 3 presents data on L. R., a twenty-four year old woman with rheumatic heart disease and mitral stenosis, who was markedly edematous, hyponatremic and oliguric, and exhibited tachycardia and indications of digitalis intoxication, including multiple, multifocal ventricular contractions, superimposed upon a basic sinus rhythm. Previously, frequent injections of mercurial diuretics, following administration of ammonium chloride, had not produced diuresis. During the preceding three weeks the patient had had increasing congestive failure, oliguria, anorexia, nausea and vomiting. Because of the gastrointestinal symptoms and the ventricular premature contractions, digitalis had been withheld intermittently.

When admitted to the metabolic ward thirty-six hours prior to day 1 (Fig. 3), she was desperately ill. The next day an infusion of 1,200 ml. of aminosol in 10 per cent glucose in water, containing 53 mEq. of potassium chloride, was administered slowly. On day 1 another 1,000 ml. of aminosol in 10 per cent glucose in water were slowly infused, followed by 1,500 ml. of 10 per cent dextrose in water, containing 53 mEq. of potassium chloride, in an effort to correct possible dehydration in the presence of edema. When no increase in urine output occurred, 300 ml. of 5 per cent sodium chloride (257 mEq.) were infused at a rate of 2 ml. per minute. At the start of the infusion of con-

centrated salt, 2 ml. of mercaptomerin also was given intravenously but, as before, no diuresis resulted. Although nausea had subsided somewhat, body weight had increased 2.6 kg. by the next morning and, as a result of the greater retention of water than sodium, the serum sodium concentration had fallen to 121 mEq./L. On day 2 parenteral fluids were limited to 300 ml. of 5 per cent sodium chloride, diluted with 100 ml. of 50 per cent dextrose in water. As a consequence of the relative fluid restriction and the concentrated salt administration, the serum sodium rose somewhat without increase in urine volume.

During the course of the potassium chloride-containing infusion on day 1, ventricular premature contractions almost disappeared, and 0.50 mg. of digoxin was given slowly, intravenously, with the remaining solutions. On day 2 oral administration of a mixture of organic potassium salts was begun. Because no ventricular premature contractions were noted, the digoxin dose was increased to 0.25 mg. orally three times daily at six-hour intervals, each dose being withheld until the cardiac rhythm had been evaluated. The failure of such therapy to precipitate the ventricular premature systoles present two days before suggested that the previous arrhythmia represented not overdigitalization, but increased sensitivity to digitalis, secondary to myocardial potassium depletion [*11*]. Therefore, 1.5 mg. of digoxin was given cautiously in divided doses during days 3 and 4.

When adequate digitalization and resulting improved cardiovascular function were achieved, the urine volume increased. As a result of the diuresis of water in excess of sodium, the body weight fell and the serum sodium increased to 130 mEq./L. However, because of the reappearance of ventricular premature contractions the digoxin dose was reduced to 0.25 mg. once daily on days 6 and 7, and twice daily on day 8. By day 9 escape from digitalization occurred, the rise in cardiac rate being accompanied by decreased urine volume, weight gain, and decreased serum electrolyte concentrations. Once again the patient was "titrated" with digitalis given at four-hour intervals, depending upon the apical rate and rhythm, checked electrocardiographically. With the aid of 90 to 150 mEq. of supplementary organic potassium salts administered daily, this procedure permitted maintenance of a regular sinus rhythm at a rate of 70 to 80 per minute. The urine volume promptly increased and remained high. As the body weight continued to fall, the serum sodium level gradually returned to normal levels.

Comment: The return of this patient's serum sodium concentration to normal after adequate digitalization was not due to cumulative retention of the small amounts of sodium in the diet inasmuch as the sodium balance remained negative, except on day 11 when escape from digitalization precipitated increased failure. It is of interest that, in contrast to the earlier "mercurial resistance," administration of a mercurial diuretic on day 9, after redigitalization, elicited a moderate natriuretic and chloriuretic response. In this patient who was in chronic congestive failure, the marked antidiuretic response, leading to persistent retention of water despite the expanded volume and hypotonicity of the body fluids, was unaffected by the administration of concentrated salt solutions, but promptly abated once the increased disproportion between cardiac output and body metabolic needs had been corrected by adequate redigitalization following potassium repletion.

During the succeeding months the serum electrolytes remained normal, although the patient received several courses of vigorous ammonium chloride, mercurial-aminophyllin therapy. At one time, however, a severe respiratory infection was associated with weight gain and fall of the serum sodium to 128 mEq./L., with return to normal following treatment with antibiotics.

Pitressin-Induced Dilution Hyponatremia. Nine weeks after the preceding study, with patient L. R. still maintained on the low sodium diet, an effort was made to reproduce the spontaneous antidiuretic sequence by the daily administration of 5 units of pitressin tannate in oil administered intramuscularly for six days. As indicated in Figure 4, the urine volume fell and, due to retention of water without sodium, the body weight rose and the serum sodium level gradually declined to 120 mEq./L. With the increasing edema, dyspnea and other symptoms of congestive failure were exaggerated. The eosinophil count fell markedly.

During the first twenty-four hours following the final injection of pitressin, profuse water diuresis resulted in a urine output of 6 L., a 2.6 kg. fall in body weight, and rapid return of the serum electrolyte concentrations to normal. The body weight, however, remained above the

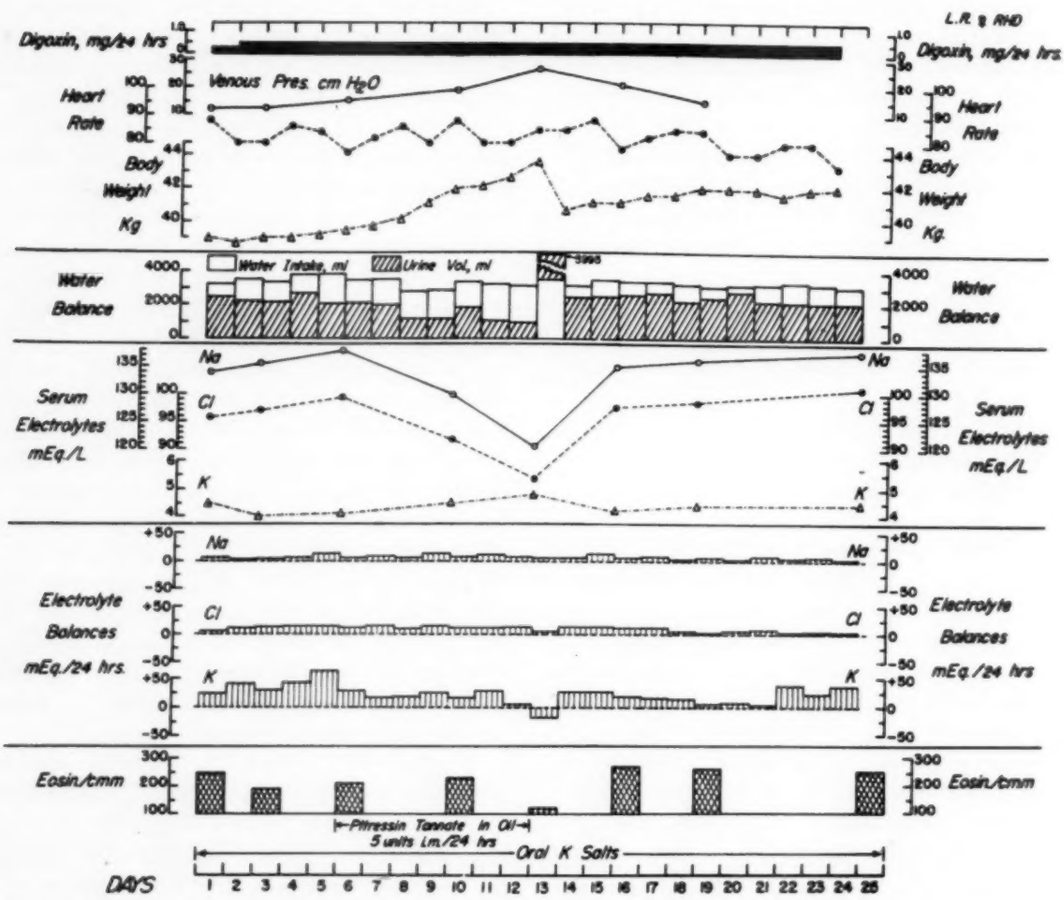

FIG. 4. Water retention and hyponatremia, following administration of pitressin tannate in oil to patient L. R.

control level as a consequence of the slightly increased sodium retention during the period of increased stress. Immediately following the profuse water diuresis, as signs of congestive failure diminished, the patient improved symptomatically. The eosinophil count returned to normal levels.

Calculation of the changes in extracellular and intracellular sodium, potassium and fluid distribution during the periods of spontaneous water retention and subsequent recovery in patients E. W., J. M. and L. R., and the period of pitressin antidiuresis in patient L. R., suggest that the changes in extracellular electrolyte concentration resulted from dilution and contraction of the body fluids by retention or excretion, respectively of water, partitioned between intracellular and extracellular spaces in accord with the Darrow-Yannet concept [*12*]. Moreover, there apparently were no significant shifts of sodium and potassium between the two major body fluid compartments. However, during periods of most severe congestive failure in these patients, as in others studied in this laboratory, evidence of increased catabolism was noted in the form of negative nitrogen, phosphorus and potassium balances [*13*], the last less often because of increased potassium intakes.

COMMENTS

The primary retention of water and the secondary hyponatremia demonstrated by these three subjects serve to illustrate a sequence repeatedly observed in patients with congestive heart failure on a low sodium intake, when the imbalance between cardiac output and body metabolic needs has been acutely intensified by either insidious or obvious escape from digitalization, or by the development of severe infection, active rheumatic fever or digitalis intoxication. An acute antidiuretic mechanism

is invoked which leads to retention of water in excess of sodium.

As a consequence, if fluid intake is maintained, continued oliguria leads to weight gain, increasing edema, azotemia, hyponatremia and hypochloremia. This clinical picture of severe congestive failure with dilution hyponatremia resembles the cardiovascular-renal dysfunction associated with severe sodium depletion in both normal and cardiac subjects [*14*]. Failure to differentiate the dilution type from the depletion type [*15*] of hyponatremia has led to misguided efforts to correct the assumed sodium deficit by intravenous administration of concentrated salt solution, which is rarely of benefit. The resulting additional expansion of the excessive extracellular fluid and plasma volumes only further aggravates the severe congestive failure and may hasten the patient's death.

It should be emphasized that mercurial diuretics cannot remove sodium from the body in excess of water and thus produce depletion hyponatremia. The sodium concentration of the urine excreted following administration of mercurial diuretics is significantly below serum levels in patients in congestive failure, due to the activation of distal tubular, base-conserving, ion-exchange mechanisms [*10*]. However, frequent use of mercurials, by decreasing the total extracellular sodium, may contribute to the fall in serum tonicity, resulting from continued primary water retention between diureses.

The increased clinical recognition of dilution hyponatremia in recent years reflects the wider application of the low sodium diet with a liberal fluid intake, and more vigorous diuretic therapy. It is obvious that the less sodium made available in the diet, the less effective will be the mechanisms activated to promote compensatory sodium retention, as water retention and dilution continue. However, water retained without sodium is distributed throughout all the body fluids, the major part shifting into cells to maintain osmotic equilibrium as the serum tonicity falls. Although increased sodium intake may restore more normal serum solute concentrations, the proportionally greater expansion of the extracellular fluid and plasma volumes may further increase the degree of congestive failure.

The precise mechanism leading to this continued water retention, despite decreasing body fluid tonicity, has not been established. As Verney clearly demonstrated [*16*], the osmoreceptor response to small decreases in extracellular tonicity normally leads to inhibition of posterior pituitary antidiuretic hormone production, with resultant water diuresis until normal serum osmolarity is reestablished. The absence of a normal diuretic response to oral or intravenous water loading in severe congestive failure, as in adrenal cortical insufficiency, suggests that antidiuresis is maintained under these circumstances by some mechanism superseding the osmoreceptors [*17*].

It has been postulated that, because of the increased titres of antidiuretic material in their urine and plasma, primary water retention in patients with cardiac and hepatic edema reflects decreased hepatic capacity to inactivate circulating antidiuretic hormone. However, it is now well established that most cardiac patients can readily inactivate physiological amounts of circulating endogenous or exogenous antidiuretic hormones [*18,19*]. On the other hand, patients in very severe congestive failure, when given intravenous dextrose in water solutions at too great a rate, may actually exhibit decreased urine flows. Because of these observations it was suggested that the primary water retention in severe congestive failure results from sustained production of posterior pituitary antidiuretic hormone, invoked by a mechanism other than, and presumably independent of, the osmoreceptor control system [*19*]. Verney's original studies suggested the existence of one such mechanism [*16*]. Thus, well hydrated dogs, during water diuresis, exhibit antidiuretic responses to loud noises, painful stimuli and other sensory stimulation. Moreover, the regulatory influence of the central nervous system on posterior pituitary function is well recognized [*20*]. Therefore, the sustained production of antidiuretic hormone in cardiac patients may be a response to the continued stress of increased congestive failure, similar to that responsible for the water retention following major surgery [*21*]. However, except in patients with heart disease [*22*] or uncorrected electrolyte depletion [*23*], such postoperative water retention is of short duration [*21*].

The more prolonged operation of an antidiuretic mechanism, independent of osmoreceptor control, was demonstrated by McCance and his colleagues who subjected normal persons to severe sweating while on low sodium intakes [*24*]. In addition to electrolyte retention, these salt-depleted subjects exhibited thirst and continued water retention, despite a significant fall in serum sodium concentration and tonicity.

Since then, many studies on the effect of acute experimental expansion and contraction of the body fluids have indicated that regulatory mechanisms function in normal subjects to preserve the volume, particularly, of the extracellular fluid, regardless of the consequent changes in tonicity [*25–28*]. The possibility that these mechanisms which can influence sodium and water excretion independently may play a role in the pathogenesis of edema and hyponatremia of hepatic, cardiac and renal disease has been repeatedly considered [*29–32*].

Although the increased salt and water retention occurring in these edematous states has been attributed to changes in blood volume, or effective circulating volume, *per se* [*29,30*], more recent investigations indicate that the common denominator is a change in effectively circulating volume; that is, some more dynamic aspect of circulation [*19,31,33*]. That this may well be the case is supported by observations on patients in congestive failure, in whom expansion of the blood volume may lead to further cardiovascular embarrassment, antidiuresis and dilution hyponatremia, whereas contraction of blood volume, with consequent improvement in circulatory dynamics and cardiac output, may be followed by prompt increase in urinary water excretion [*19*]. Although in congestive failure the trigger mechanism may be related to change in cardiac output, the actual stimulus may be altered hemodynamics of some baro- or chemoreceptor in the cephalad portion of the circulation [*25,31,32,34*].

The increased titres of vasodepressor material (VDM or ferritin) found in the blood of patients in severe congestive failure [*35*] may also mediate water retention. Baez and his colleagues have demonstrated that injections of ferritin in normal dogs, but not in dogs with diabetes insipidus, lead to marked antidiuresis [*36*]. Livingston [*37*] has observed similar antidiuresis, with a rise in urinary total solute concentration, in normal human subjects given ferritin. Therefore, increased circulating VDM may in some way stimulate the posterior pituitary release of antidiuretic hormone despite hypotonicity of the body fluids. In mild to moderate congestive failure, the degree of hepatic ischemia and anoxia may not be severe enough to result in critical levels of VDM production. In advanced congestive failure or when failure is intensified, as in the patients described in the present report, circulating levels of VDM may be sufficient to invoke increased antidiuretic hormone production.

Recently, it has been suggested that the impairment of glomerular filtration rate in congestive failure may in some way contribute to the retention of water in excess of sodium [*38*]. Although it is true that the maximal water diuresis achievable in a given subject will be determined in part by the filtration rate and that extreme reduction in glomerular filtration may prevent adequate water diuresis [*39*], we have demonstrated that this antidiuretic mechanism may be invoked in patients with only moderate reduction in glomerular filtration [*19*]. Therefore, the excessive water retention of patients in severe congestive failure may also represent sustained production of hypophyseal antidiuretic hormone.

In contrast to the more acute dilution hyponatremia, cardiac patients may demonstrate an asymptomatic hyponatremia which often appears more or less gradually during treatment with adrenal cortical steroids, cation exchange resins [*8*] or other diuretics [*14*]. Under these circumstances, often without gain in weight or other evidence of primary water retention, the serum concentrations of sodium and solutes may gradually fall. Conversely, cessation of the specific therapy is associated with a gradual return of body fluid tonicity to normal levels, without increased water excretion, significant potassium retention, or loss in body weight. The usual metabolic calculations suggest that shifts of sodium have occurred between the extracellular fluid and some other compartment [*40*].

In other patients, particularly those subjected to prolonged or repeated periods of ammonium chloride acidosis before injection of mercurial diuretics, the serum sodium concentration may gradually fall to levels of 125 to 130 mEq./L. Observations from several laboratories [*40*] confirm the report of Cort and Matthews [*41*] that, following correction of potassium depletion by increasing the potassium intake, there is a gradual rise of serum sodium and total solute concentrations to normal. This sequence may represent the more rapid development of intracellular electrolyte depletion and the secondary readjustment of the osmoreceptor-posterior pituitary system, postulated to explain asymptomatic hyponatremia of a more chronic nature.* How-

* The evaluation of hyponatremia in a given patient in congestive failure is complicated by the existence of another clinical syndrome with body fluid hypotonicity,

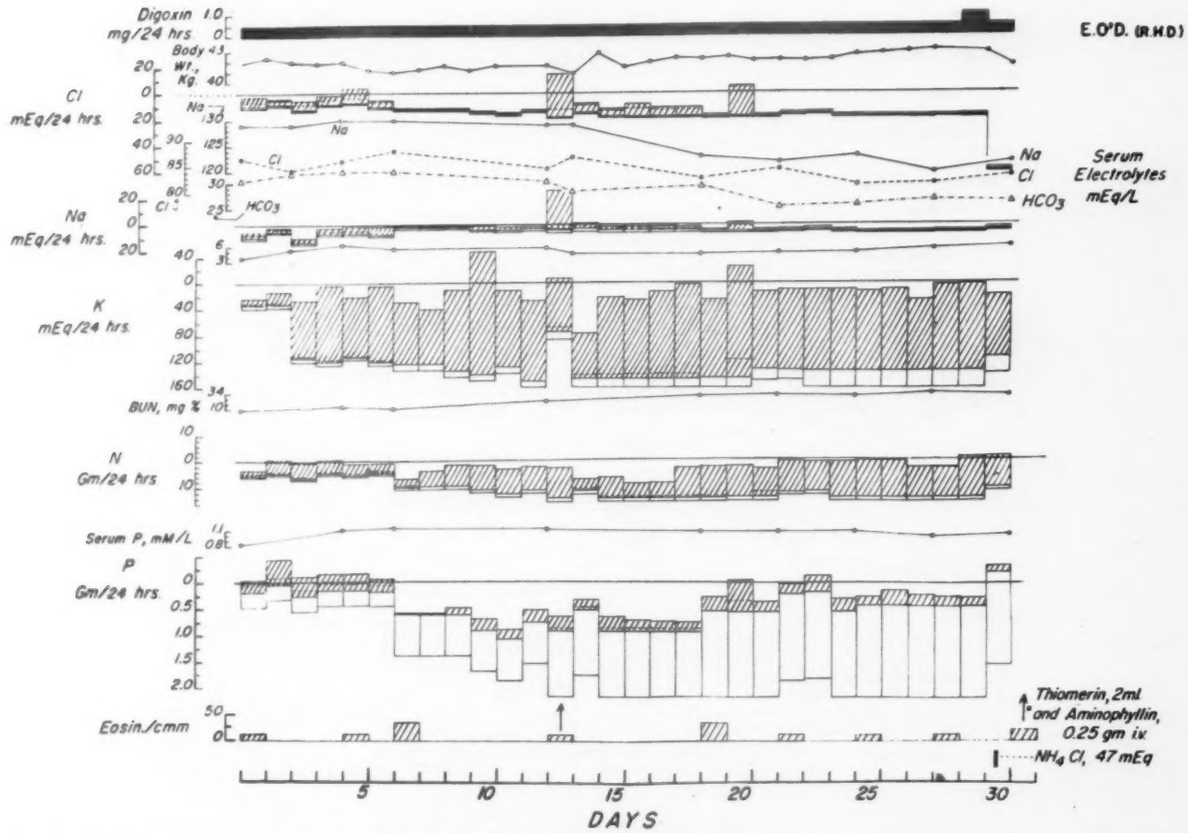

FIG. 5. Progressive increase in body weight with a fall in serum sodium concentration due to continued water retention in the terminal phase of congestive heart failure in a patient (E. O.) on a low sodium intake. Death occurred on day 31.

ever, it is well documented [*22*] that patients in chronic congestive failure often exhibit severe intracellular potassium depletion, resulting from poor nutrition, vigorous diuretic therapy, chronic tissue ischemia and hypoxia and/or, perhaps, increased levels of circulating adrenal cortical steroids. Generally, the serum potassium concentrations are normal and may even be elevated.

The treatment of hyponatremia has been previously reviewed [*14,40*]. Success in this difficult task depends less upon laboratory diagnostic tools than upon an understanding of the underlying pathogenesis. In evaluating the individual case, review of the patient's recent clinical history is of the utmost importance. Careful search must be made for factors known to precipitate acute water retention with dilution hyponatremia. In our experience, the most common correctable factor has been inadequate digitalization, however produced. Often this is undetected because of the presence of electrocardiographic changes interpreted as "digitalis toxicity" but actually reflecting, not over-digitalization, but intracellular potassium depletion or some other myocardial metabolic derangement.

i.e., chronic asymptomatic hyponatremia. This is a state not infrequently observed in many chronic illnesses, particularly those characterized by some degree of malnutrition, such as tuberculosis [*42*], anorexia nervosa, panhypopituitarism [*43*], starvation, cirrhosis and chronic congestive failure [*14*]. Characteristically, the hyponatremia and hypotonicity of the body fluids in such patients do not contribute significantly to the underlying clinical picture and are extremely resistant to therapy. For example, no impairment of water diuresis in response to oral or intravenously administered water loads is noted. Similarly, augmentation of oral salt intake or intravenous administration of concentrated sodium solutions results in increased water retention and increased sodium excretion until the previous hypotonicity of the body fluid is restored. Thus it would appear that the body has become adjusted to the hypotonic state and resists any deviations from the low serum electrolyte concentration by evoking mechanisms which ordinarily protect the normal body fluid tonicity and volume. Although the precise biochemical definition of this altered response has not been delineated as yet, the most reasonable explanation would appear to be some change in intracellular fluid and electrolyte distribution corresponding to, and probably preceding, the reduction in extracellular tonicity.

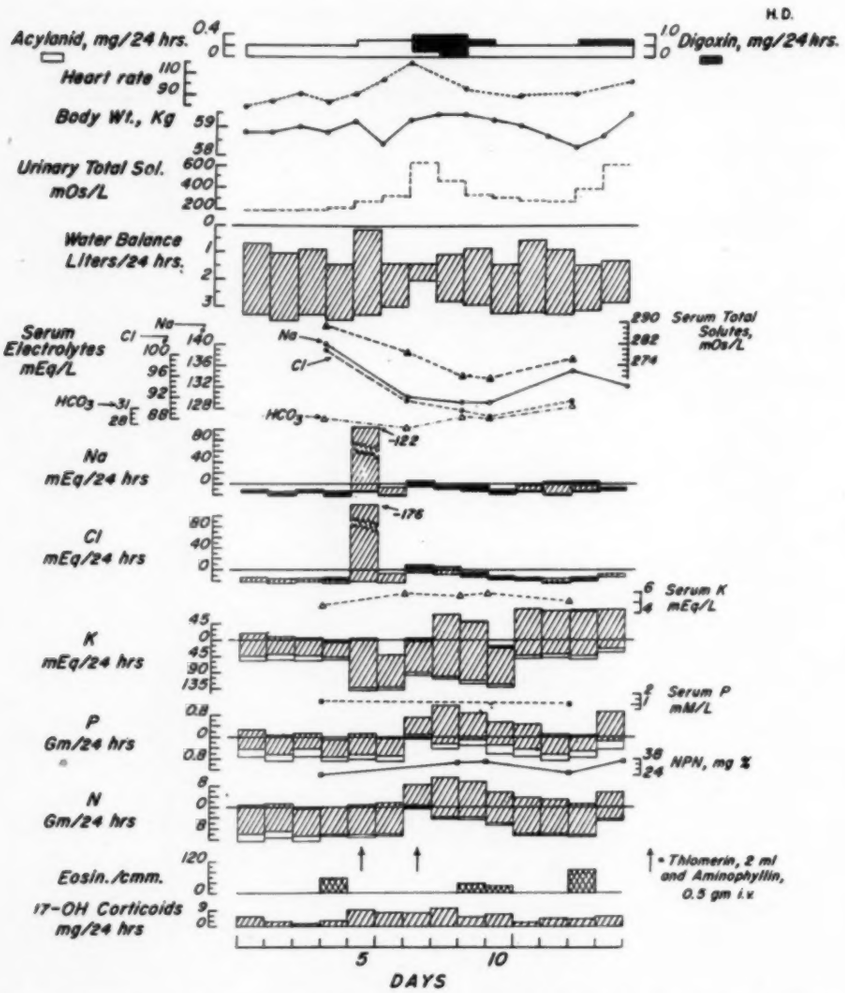

FIG. 6. Continued water retention and hyponatremia in a patient (H. D.). Note moderate, temporary increase in urine volume with slight rise in serum electrolyte concentration as the pulse rate decreased following cautious parenteral redigitalization. Death occurred on day 15.

In other cases, hidden infection, unsuspected pulmonary infarction, active rheumatic fever and, most often, progressive deterioration of myocardial function in the terminal phases of chronic congestive failure have been responsible for dilution hyponatremia. Many patients in chronic congestive failure are encountered who, despite severe sodium restriction, adequate digitalization, large doses of potassium salts, and efforts at nutritional rehabilitation, inexorably follow a downhill course to death. Unless fluid intake is carefully adjusted to excretion and bodily needs, there is a progressive rise in body weight and a fall in serum electrolyte levels. (Figs. 5 and 6.)

It has been stated that under these circumstances administration of adrenal cortical steroids is beneficial [*44*]. In our experience, large doses of corticotropin, cortisone, hydrocortisone and prednisone do not affect the clinical course, unless active rheumatic fever or some other underlying inflammatory process is thereby suppressed. In fact, the increased levels of adrenal cortical steroids in patients in severe congestive failure, on low sodium intakes, may conceivably lead to more marked failure, by expanding the extracellular fluids at the expense of the intracellular and transcellular fluids, as has been described in normal subjects [*45*] and in patients with advanced collagen diseases [*46*]. Figure 7 illustrates such a sequence in a patient with rheumatic heart disease in whom mild

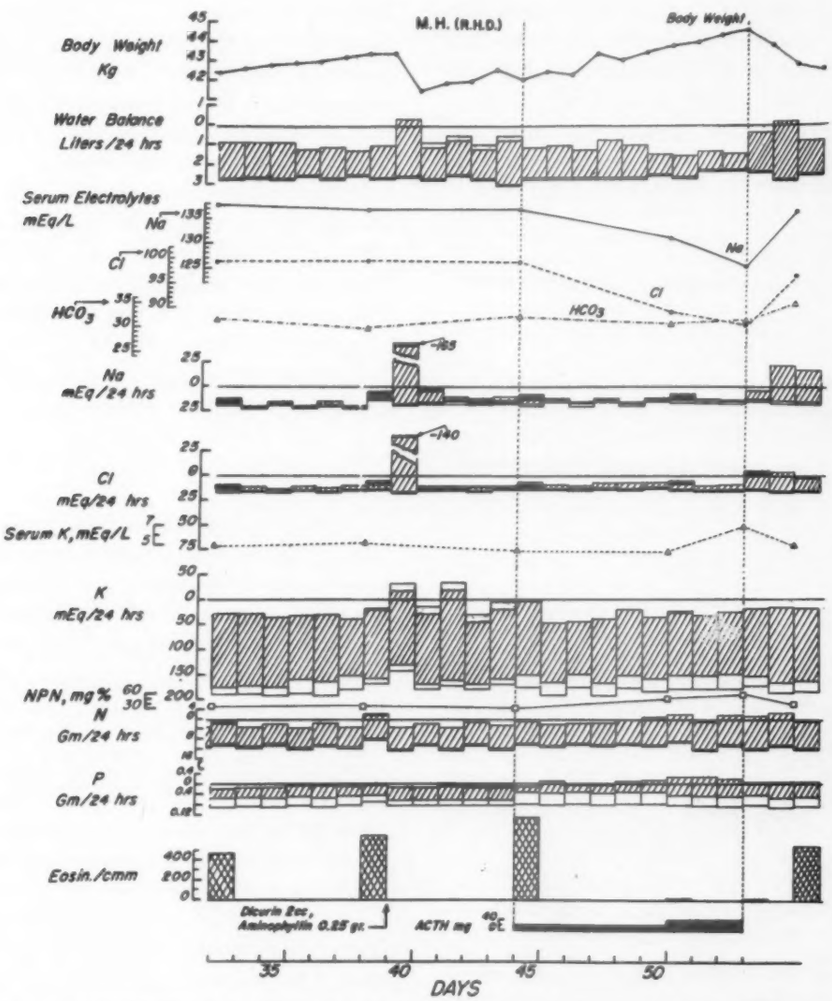

FIG. 7. Development of increased congestive failure, water retention and hyponatremia during administration of corticotropin to a cardiac patient (M. H.) on a low sodium intake. Note prompt recovery on cessation of ACTH therapy.

dilution hyponatremia had previously developed, following escape from digitalization. Administration of corticotropin, with virtually no pitressin titre, led to exacerbation of the signs of congestive failure and increasing water retention, rise in body weight, and fall in serum sodium level, with prompt return to control levels following discontinuation of corticotropin.

It was recently reported that correction of abnormally low serum sodium concentrations (in only a few of a large number of patients) in chronic congestive failure was achieved by vigorous mercurial diuresis, following an acidifying pretreatment regimen [*47*]. The results were attributed to the hypotonic concentrations of sodium in the urine, in comparison with the serum, during diuresis. Actually, in our experience, such vigorous mercurial diuresis rarely if ever corrects hyponatremia in a cardiac patient, unless the resulting reduction in extracellular fluid and plasma volume *per se* diminishes the load on an already overburdened circulation. Under the latter circumstances the resulting increase in cardiac output [*19*] interrupts the antidiuretic mechanism and leads to water diuresis and further weight loss, in contrast to the increased water retention which ordinarily follows contraction of the extracellular fluid by mercurial diuresis [*48*].

The well known failure of concentrated sodium infusions to affect the ultimate clinical course of hyponatremic patients in severe congestive failure is depicted in Figure 8. This patient, a forty-two year old man with rheumatic

heart disease, exhibited not only pulmonary congestion and massive peripheral edema but also hyponatremia and anorexia. No signs of infection, pulmonary infarction or active rheumatic fever were demonstrable. Cautious administration of supplementary potassium salts

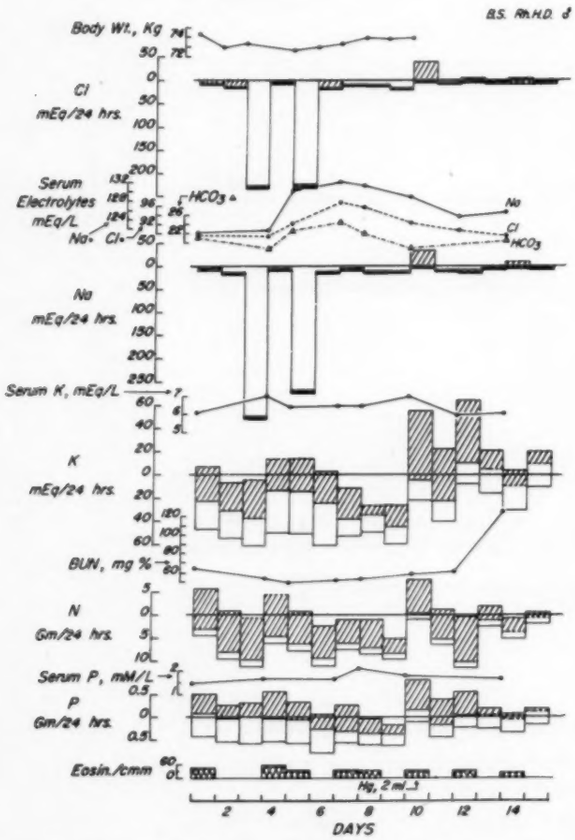

FIG. 8. Failure of infusions of concentrated sodium solutions to reverse the terminal phase of congestive failure in a hyponatremic cardiac patient (B. S.). Death occurred on day 15.

was discontinued, because his serum potassium level rose to 7 mEq./L. Efforts to increase the dose of digoxin resulted only in ventricular premature contractions. Therefore, on days 3 and 5, large amounts of hypertonic sodium chloride-sodium lactate mixture were given intravenously, with a rise in serum sodium concentration to 133 mEq./L. However, the increased serum tonicity led only to intensification of congestive failure. Despite reduction in fluid intake, the body weight continued to rise, the body fluids were slowly re-diluted, and death occurred ten days later.

Although great advances have been made in the management of "intractable" congestive failure, reversal of the steadily downward course illustrated in Figures 5, 6 and 8 is extremely difficult. Experience has established that only reduction of the disproportion between cardiac output and body metabolic needs can promote water diuresis, mobilization of edema and restoration of more normal body fluid tonicity [6]. When this cannot be accomplished, as in terminal cardiac patients, exitus may be anticipated. Prior to this stage, efforts should be made to find some cause of worsening of the underlying congestive failure. If the search is successful, gratifying therapeutic results may be achieved, as the present study indicates.

SUMMARY

Acute intensification of chronic congestive failure in cardiac patients on low sodium diets may lead to continued water retention, with increasing edema and hyponatremia without external loss of sodium. This sequence is illustrated by the events following development of severe respiratory infections or escape from digitalization in such patients. Such a sequence may occur also, at times, in the presence of electrocardiographic changes suggestive of digitalis toxicity but actually due to potassium depletion.

This clinical course is not favorably influenced by intravenous administration of either isotonic or concentrated sodium solutions. However, increasing cardiac output by adequate digitalization or decreasing bodily metabolic demand by treatment of the underlying infection may lead to increased excretion of water in excess of sodium, decreased body weight, and restoration of more normal serum electrolyte concentrations.

This sequence of events is attributed to sustained production of antidiuretic hormone, invoked by some extraosmoreceptor mechanism, whenever the cardiac output becomes inadequate for the body's metabolic needs. The more protracted operation of this mechanism is illustrated by the progressive water retention and hyponatremia frequently observed in patients on a low sodium diet and unrestricted water intake during the terminal phase of congestive failure. A fatal outcome may be anticipated unless the cardiac output can be increased or the burden on the impaired circulation in some way diminished.

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Hereditary Sensory Radicular Neuropathy and Other Defects in a Large Family*

Reinvestigation after Twenty Years and Report of a Necropsy

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STUDY of a family in 1937 revealed a variety of hereditary defects occurring singly or combined in twenty of 234 recorded members [*1*]. In one branch, sixteen of thirty-seven persons were affected. Dermal or sensory defects alone were noted in eight. Five men and two women had dermal sensory defects and plantar ulcers; of these, pedal osseus necrosis and extrusion of fragments of bones were present in four, the hands were less severely involved in one, and a harelip and cleft palate noted in another. Loss of sensation usually was inapparent for years, but came to the victim's attention after a painless injury or was detected by examination. The wounds either healed, or ulceration, penetration and osseus necrosis followed after the age of eighteen. Two women had epileptiform seizures. Four others had harelip with or without cleft palate. Except for harelip and cleft palate in one member, no defects had appeared in the fifth generation, but were predicted. In the absence of diagnostic-anatomic proof, the trait was ascribed to dysgenesis of the central nervous system, probably myelodysplasia.

Opportunity arose to re-examine the severely afflicted branch of the family after twenty years to learn the fate of those who exhibited abnormalities and to detect early evidence of neural disturbance or other defects in members of the fourth, fifth and sixth generations. All living descendents of B-13 of the reconstructed tree (Fig. 1) were examined except children less than two years old and a few too remote to visit. Information about the latter was obtained by inquiry.

In the twenty-year period additional defects

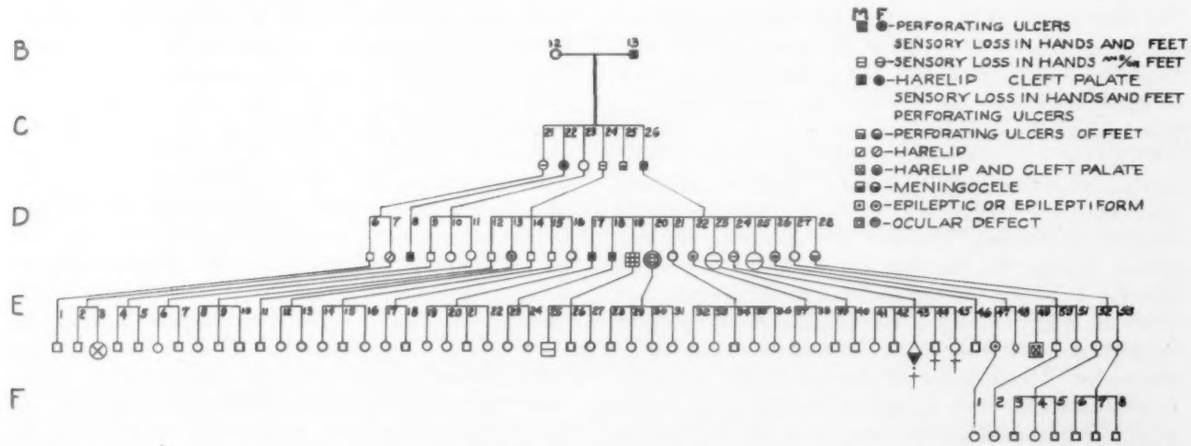

FIG. 1. This tree is patterned after the original one [*1*] except for omission of generation A and of unaffected familial branches and the addition of members of generations E and F born since 1937. New symbols are added to include involvement of the hands, ocular defects and overt congenital neural malformation. Previously observed victims are indicated by small symbols; members in whom defects appeared in the twenty-year interim have similar but large ones.

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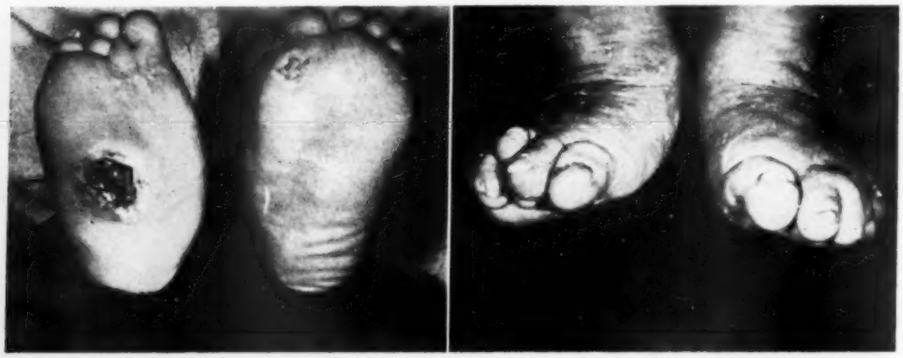

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FIG. 2. C-22 (M. J.). Penetrating ulcers on both soles, healed ulcer at base of first and second right toes and at base of left great toe.

FIG. 3. C-22 (M. J.). Severe deformity of feet (pferd fuss).

had appeared in patients previously described, and, as anticipated, new ones had emerged or were discovered by examination in six members free of stigmas in 1937 or born since then. In Fig. 1 the new members are graphically distinguished by larger symbols. Only twelve members of generations E and F are now more than sixteen years old and one already has a premonitory sensory defect at seventeen years of age. The rest are too young for the usual onset of neuropathy. Two were born with harelip and cleft palate, and one was anencephalous. Restudy after another twenty years will show whether or not some of the defects prevalent in generations C and D are being bred out.

FATE OF PATIENTS OBSERVED IN 1937

C Generation. C-21 (A. D. G.) had had diminished tactile and thermal perception of the great toes and hyperactive knee jerks but has remained well. Her daughter D-7, has harelip and her granddaughter, E-3 has harelip and cleft palate.

C-22 (M. J.), sixty-three years old, had multiple defects. Repeated pedal ulceration began at age forty, later than the others, and has progressed to osseus necrosis of the feet. The feet are anesthetic; hypesthesia extends to the mid-calves and diminished thermal perception to the mid-thighs. In the past five years the fingers have become anesthetic, and there is hypesthesia and blunting of thermal sensibility up to the wrists. The muscles of the hands are atrophic. Senile cataracts have appeared. Photographs of the patient's feet with penetrating ulcers and deformity (pferd-fuss), and roentgenograms are shown in Figures 2, 3 and 4.

A son, D-8, with harelip and cleft palate died at birth. According to new information, his brain was said to have been exposed (meningocele?).

C-24 (D. D.) died at the age of sixty-five with no progression of the sensory impairment originally described. His daughter, D-13, died of "epilepsy" at age twenty-eight. A grandson, E-15, age eight, has scoliosis.

C-26 (A. D.), father of D-17 and D-18 who were the chief subjects of the previous report [*1*], was obese. Both legs and several fingers had been amputated but he led an active life until the onset of terminal cardiovascular renal disease. After his death in 1952 at the age of sixty-seven, necropsy was performed, one of the few made in such a patient. Pertinent details were extracted from a report kindly furnished by Dr. C. E. Rodriguez, pathologist at the Wilkes-Barre General Hospital, as follows: Death was caused by pneumonia, severe generalized arteriosclerosis, hypertensive cardiovascular disease and nephrosclerosis. The skin over the stump of one leg was ulcerated. In sections of the area there were thickening and fibrosis of the nerve fibers and blood vessels. Similar changes were present in the vessels of a deformed terminal phalanx, resembling thromboangiitis obliterans. There was no deformity of the vertebral column. The cord from the cervical portion to the cauda equina appeared to be normal except for a few grayish plaques (0.5 cm.) on the posterior surface in the mid-thoracic region. The cord was firm throughout and without evidence of myelodysplasia, heterotopia or syringomyelia. Portions of the cord were examined by Dr. Bernard J. Alpers of Philadelphia who kindly submitted the following report: "In sections of the thoracic cord there was demyelinization of the nerve roots and of the posterior columns sharply limited to the columns of Goll. In tissue stained with toluidine blue, there was some internal proliferation of the pial blood vessels. There was no evidence of inflammation. The cells of the anterior horns stained darkly and were attenuated, but in most the Nissl substance was preserved and the nuclei were located centrally. In sections of the lumbar cord, demyelinization of the nerve roots was severe, especially in the posterior ones.

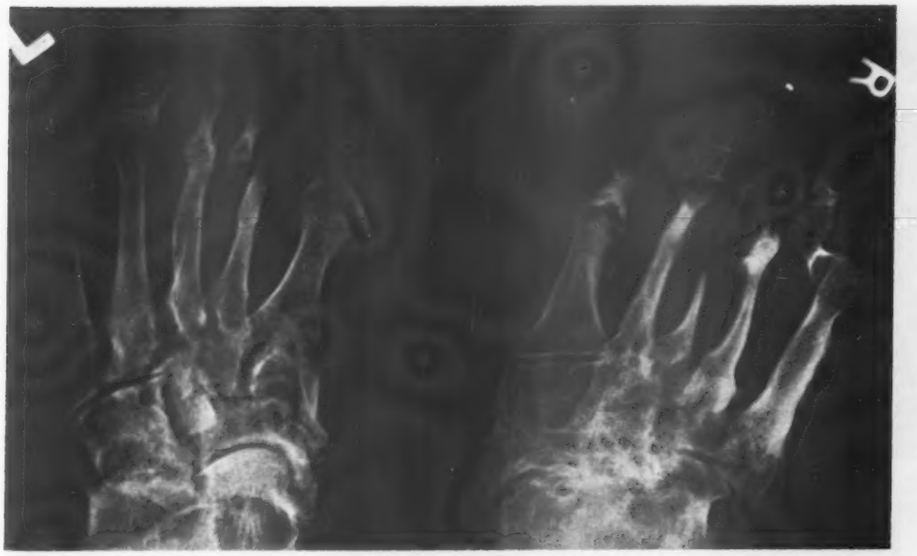

FIG. 4. C-22 (M. J.). Right foot. There is edema about the ankle. Many of the tarsal joints are obliterated partially or completely. Cystic changes appear in the tarsal bones, particularly in distal ones. There is subperiosteal osteogenesis and thickening of the cortex of the fifth metatarsal, and almost complete disarticulation of the proximal phalanx. The fourth metatarsal is narrowed, the shaft of the third almost completely gone, and the second is thickened and fused with the phalanx. The first is shortened and degenerated at the joint with the phalanx. Phalanges are disarticulated, partly absorbed and the joints are fused. Left foot: Disarticulation and fusion at the second and third metatarsal-phalangeal joints. There is severe degeneration at the first metatarsal phalangeal joint. Astragalus and calcaneus are intact. The remainder of the tarsals show varying degrees of cystic degeneration and fusion, not so severe as in the right foot. The phalanges are displaced laterally at the second metatarsal level. There is disarticulation of the fifth phalanges. These logograms were made by the courtesy of Dr. Elmer St. John.

There was similar change in the posterior columns, more in the lateral portion near the zone where the roots entered. The anterior horn cells stained feebly and their nuclei were eccenteric. A number of cells showed central chromatolysis. Pial blood vessels stained with toluidine blue were thickened." The lesions, he believed, were consistent with those of hereditary sensory radicular neuropathy.

D Generation. D-17 (H. D.), forty-seven years of age, had progressive ulceration and osseus necrosis of the feet terminated by bilateral amputation below the knees in 1941. He is active and ambulatory but suffers repeated transient ulceration of the stumps from friction of the prostheses. At present, he cannot feel pinpricks on his legs and in a large irregular patch on the left side of the abdomen. Perception of heat is delayed in these areas. Numbness of both hands began in 1941 and repeated small, transient ulcers occurred eleven years later. He can discern heat slowly and has had several burns. Absent to diminished sensitivity to pinpricks in the left hand and arm extends to the elbow except for a V-shaped patch on the flexor surface with its base at the elbow. Sensation is absent in the right hand and arm but increases slightly toward the shoulder and extends over the shoulder and right scapula.

For three years, except for a few days, he has had continuous pain across the upper part of his back, more on the right side. This is the only instance of pain of that type noted in the family. There have been three episodes of violent pain lasting about fifteen minutes, the first in 1951, so severe that a shock-like state resulted. Pain involved the right suprascapular and cervical region and there was loss of sensation and numbness in the right hand, arm and right side of his face which resumed its usual degree after five days. Two succeeding episodes, the last in 1957, were less severe but recovery took longer and after each one permanent hypesthesia advanced proximally.

He has had six episodes of unexplained hematuria. During one spell of "nervousness" his systolic blood pressure, usually 118 mm. Hg, rose to 184. Roentgen therapy applied to the spine for suspected syringomyelia only resulted in severe burns which ulcerated and were excised, leaving deep scars. His four children, the eldest seventeen years of age are normal.

D-18 (R. D.) also had bilateral amputations in 1941. Dr. Alpers examined sections of a peripheral nerve in a severed leg. It was fibrotic. Roentgen therapy to the spine caused lesions similar to those of his brother. In 1950, at thirty-seven years of age, weakness and anesthesia of both hands were noted

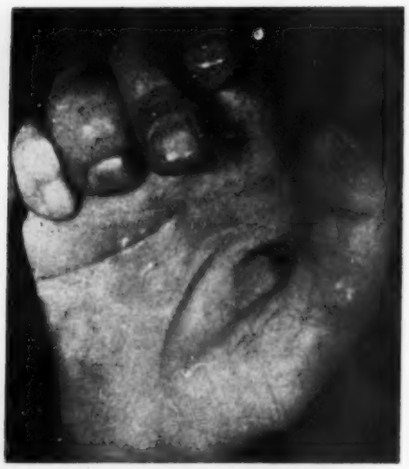

FIG. 5. D-18 (R. D.). Flexion contraction of all fingers with a healed ulcer on the base of the thumb.

and minor injuries caused repeated transient ulceration. Ulceration usually began in the interphalangeal creases and spread to the tendon sheaths, often with purulent exudate and systemic symptoms. Surgical drainage and resection of tendons were helpful but resulted in deformity, as shown in Figure 5. Roentgenographically the bones appear normal. The hands are anesthetic to the wrists. Hypesthesia and diminished thermal perception extends to the elbows, especially on the extensor surfaces.

Two daughters are normal.

D-21 (J. S.), in 1937, was noted as having dusky, cyanotic, exfoliating feet and legs, but these features subsequently disappeared. Her children are normal.

D-22 (M. H.) continues to have epileptiform spells at long intervals. She has a congenital deformity of the distal phalanx of the right thumb. Her two children are normal.

D-24 (M. M.) also had had duskiness and scaling of the feet that disappeared. There now is decreased sensation to changes of temperature. At age eighteen, a painless cigarette burn of her foot healed. A defective child, E-43, was said to have been anencephalous with an open neural tube and died at birth. Two others died in infancy probably from Rh incompatibility and two are normal.

D-26 (I. P.). Epileptiform seizures reported in 1937 have not recurred. Hypesthesia of the great toes also disappeared but now there is hypesthesia of the volar surfaces of the index fingers and hyperactive knee jerks. Her daughter, E-47, has had similar seizures and has hyperactive patellar reflexes. A granddaughter is normal.

D-27 (H. R.). Two of her children and a grandchild are normal. A defective son E-49, previously registered as having harelip and cleft palate, is nearly deaf from repeated infections of the eustachian tube. He is almost blind since early childhood from coloboma and pigmentary retinal degeneration. Supination of the arms is limited but roentgenograms show no osseus changes

There is a high incidence of rheumatic fever in the descendants of D-27 and D-28.

NEW DEFECTS IN PREVIOUSLY UNAFFECTED MEMBERS

D-19 (T. D.) was recorded as having cold, desquamating, bluish, hypesthetic feet, hypereflexia and spina bifida in 1937, at age twenty-two, but had no other trouble until the age of 25. Ulceration and osseus necrosis of the left foot began after a plantar burn caused by a prank in 1940. Numerous scrapings of the bones were futile and amputation was performed in 1941. Small ulcers appeared spontaneously on the right sole in 1947 (age thirty-two) and amputation was performed forthwith. He maintains his occupation, but friction from the prostheses causes recurrent ulcers which heal after rest.

At age forty-one, numbness and weakness of the hands appeared. There is severe atrophy of the interosseus muscles, thenar and hypothenar eminences. The skin below the knees and of the hands and wrists is anesthetic and insensible to changes of temperature. The vibration sense is intact His son, E-25, age seventeen, has diminished perception of pain and temperature of the third left toe. Two other children are normal.

D-20 (V. A.) was normal at the age of eight in 1937. At age fifteen impaired sensation of the feet was noticed. Her vision also failed but was aided by lenses. At age twenty-two recurrent, progressively larger plantar ulcers began to form, but healed slowly. At present (age twenty-eight) sensation is absent on the fifth fingers and hypesthesia extends to the wrists. Figure 6 shows edema, and deformity of second and third toes with 2 small ulcers on the left foot. There is now a large, ten-month old, penetrating ulcer of the left sole with a purulent discharge (Fig. 7), a forerunner of osseus necrosis. Roentgenograms of the left foot show evidence of early osseus involvement and dislocation. (Fig. 8.) There is anesthesia below both knees and hypesthesia from there to the hips. At present she has cataracts said to be congenital in type. Her four children are normal.

D-23 (H. W.), aged thirty, for several years has been unable to gauge the temperature of dish or bath water unless it splashed higher on her arms. She has had several painless injuries of her feet. On examination there is hypesthesia to anesthesia and diminished thermal perception in all four extremities. Two children are normal.

D-25 noted no trouble until, at age twenty-two, she sustained a severe but painless burn when her shod foot touched a hot radiator. At present there is hypesthesia and impaired sensation to temperature below the knees. The patellar reflexes are hyperactive. A son is normal.

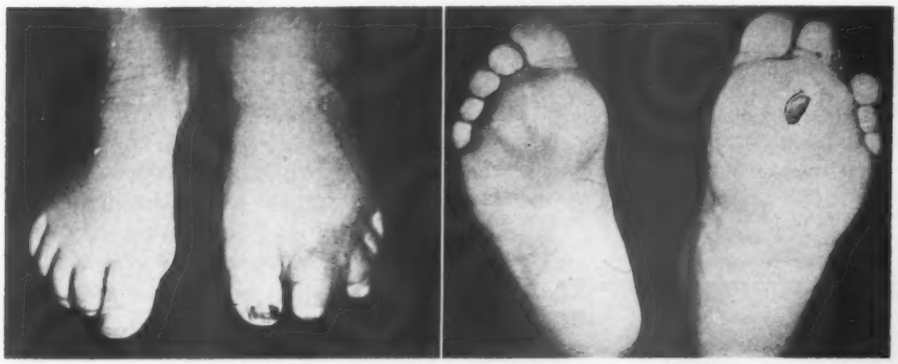

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FIG. 6. D-20 (V. A.). Edema of left foot, ulceration and deformity of second and third left toes.

FIG. 7. D-20 (V. A.). Ten-month old left plantar ulcer.

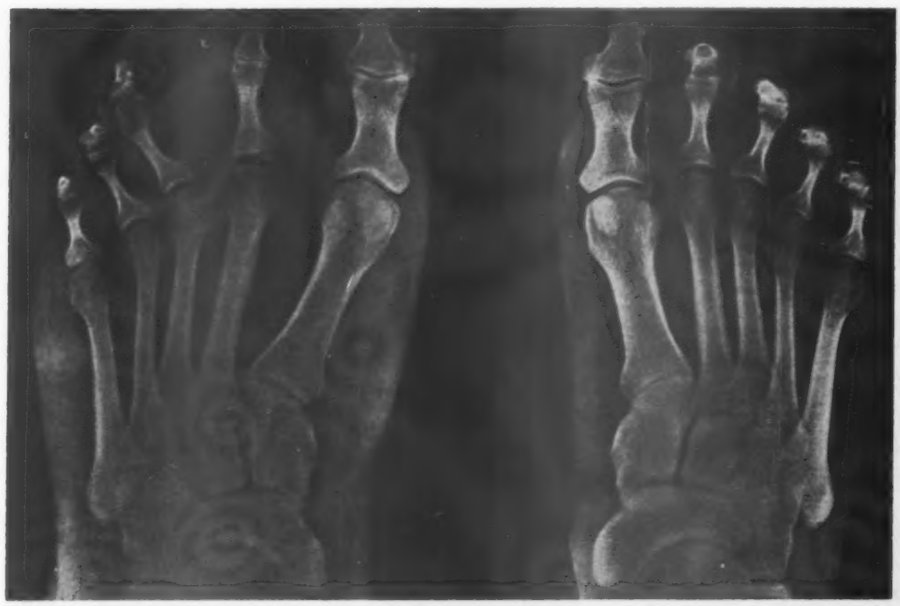

FIG. 8. D-20 (V. A.). Left foot: Severe edema; early osteoporosis of second phalanx and distal second metatarsal bones; roughening of the periosteum and subperiosteal oestogenesis. The right foot is normal. Logograms by courtesy of Dr. Elmer St. John.

COMMENT

As anticipated in 1937, hereditary defects in afflicted members of a large family have progressed and caused increased disability in the succeeding twenty years in some of them; new ones have emerged in others. In four members (C-21, C-24, D-24, D-26) sensory changes have not advanced, and in three (D-21, D-24, D-26) some of the abnormal signs have disappeared. In addition, predicted defects have come to light in four previously unaffected members of generation D (D-19, D-20, D-23, D-25), in E-25, and congenital malformations appeared in three (E-3, E-43, E-49) born after the original report was made. The incidence of defects in 1937 and in 1957 is shown in Table 1.

Obviously, the family has multiple hereditary defects of which sensory disturbance, trophic ulcers and osseus necrosis are separate, outstanding, and attributable to radicular neuropathy. Harelip, cleft palate, epileptiform seizures, ocular defects, meningocele, scoliosis and anencephaly probably result from other midline dysgenesis.

Apparently, some of the early disturbances may disappear (D-21, D-24, D-26) or remain

static. Of interest is the stepwise progression proximally of sensory changes in D-17 after repeated episodes of severe pain resembling the pain described by Hicks [*2*]. It suggests exacerbations and advancement of whatever process takes place in the roots or ganglions. His repeated hematuria and transient hypertension are unexplained.

TABLE I
INCIDENCE OF DEFECTS

Defects	In 1937	In 1957
Dermal sensory defects	12	16
Plantar ulcers	7	9
Osseus necrosis	4	7
Harelip and cleft palate	5	6
Epileptiform seizures	2	3
Meningocele	1	2
Cataracts	0	2
Coloboma	0	1
Scoliosis	..	1
Total	31	47

Of importance were lesions in the nerve roots and posterior columns of the cord in C-26. A peripheral nerve of an amputated leg (D-18) was fibrotic. Neural and vascular lesions in ulcers are discounted as secondary to chronic inflammation. Information about the condition of the nerves between the periphery and the roots is lacking.

The question may be raised, whether the osseus necrosis is the result of primary neuro-osseal trophic degeneration or of chronic osteomyelitis secondary to dermal insensibility, repeated long-standing penetrating ulcers, or to a combination of the two. There has been no fever or pain or roentgenographic changes characteristic of osteomyelitis. So far as we know, dermal anesthesia preceded overt osseal destruction or changes visualized roentgenographically in our patients. Dermal disturbances have persisted for years in the hands of D-17 and D-18 and in the right foot of D-20 without demonstrable lesions of the bones.

In a review, Van Bogaert suggests that ulcers may be the first overt indication of a progressive, hereditary, degenerative disease of the cord. The clinical signs of neuroganglioradicular involvement and mutilation may precede evidence of disease of the cord [*3*]. Yet in C-26, changes in the cord were minimal at age sixty-seven. In Girard's patient, lesions were present in the posterior nerve roots, in the sciatic nerve, but not in the cord [*4*]. Denny-Brown explains the apparent paradox of sensory dissociation of greater degree of loss of sensation to pain than to touch, and the loss of thermal perception greater than that to pain. Ordinarily this is characteristic of damage to the grey matter of the cord, but two possibilities are mentioned: (1) a loss of smaller ganglions and smaller nerve fibers means a loss of fibers regarded as those serving pain; (2) disturbances of any single nerve root or sensory ganglion causes an area of sensory loss which is more extensive to temperature and pain than it is to touch [*5*].

Epilepsy, as in our patients, was recorded in other similarity afflicted families. Deafness in Hick's patients was attributed to atrophy of the cochlear and vestibular ganglions similar to that in the spinal ganglions. It may represent a factor common to various familial neuritides [*5*]. Perhaps the ocular and other defects in our family may rest on a similar basis.

In the past, without pathologic evidence, disease with hereditary sensory changes, trophic ulcers and pedal osseus necrosis, as in the persons described here, had been named myelodysplasia, status dysraphicus, familial spinal gliosis and osseus atrophy, osteolysis of the extremities, trophoneurosis, hereditary universal acrodystrophy, and by other terms. The demonstration of lesions in the spinal ganglions, the posterior roots, the posterior columns and peripheral nerves by Denny-Brown and others clarified the problem. Similar changes were found in our patient. On the basis of the establishment of polyganglionic and radicular hereditary disease as an entity, and on lesions in his own patient, Van Bogaert suggested that most if not all examples of the disorder in question, excepting syringomyelia, should be classified as a group.

SUMMARY

In 1937 report was made of a large family afflicted with sensory changes, trophic penetrating plantar ulcers, pedal osseous necrosis, similar less severe involvement of the hands, harelip, cleft palate and epileptiform seizures. Re-examination after twenty years revealed predicted new lesions in previously described victims. New defects had emerged in the interim in several previously unaffected genetic relatives.

According to pathologic evidence, the major defect is the result of radicular and ganglionic hereditary neuropathy. Ocular disturbance, meningocele, scoliosis and anencephaly may be related or dissociated defects. Epileptiform seizures may be related or a separate hereditary trait.

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Circumstances Surrounding Complications of Cerebral Angiography*

Analysis of 546 Consecutive Cerebral Angiograms

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THE morbidity and mortality rates of cerebral angiography are still matters of debate [*1,17,22*]. Some factors leading to complications have been defined but there are still questions in regard to the contraindications and best technic of arteriography. For example, while general anesthesia has been considered to prevent complications [*1*] and to obviate reactions related to vascular spasm [*2*], it has also been considered to be the cause of arteriographic complications [*3*]. Similarly, although many studies [*1,4–10*] have concluded that complications may be reduced by use of a limited number of small injections given at considerable time intervals, another study [*11*] failed to find a direct relationship between the incidence of complications and the rapidity or the size of the injections. Again, cerebral angiography in the face of cerebral arteriosclerosis [*4*], cerebral thrombosis [*1,12*], in the "sick patient" suspected of having a subdural hematoma, and in the presence of severe neurologic disease or coma [*13*] has been considered a dangerous procedure. However, it has also been concluded that prompt arteriography is desirable in cases of intracranial bleeding [*14,22*] and in the acute stage of suspected intracerebral hematoma [*15*] in order to determine the nature of the lesion and to plan an appropriate therapeutic regimen.

TABLE I
AGE DISTRIBUTION OF 483 PATIENTS

Age (yr.)	No. of Patients
0–10	8
11–20	15
21–30	32
31–40	54
41–50	120
51–60	152
61–70	78
71–80	22
81–90	2

The experience with cerebral angiography at The Mount Sinai Hospital, New York City, did not appear to be in agreement with some of these conclusions. It was therefore decided to review and analyze the circumstances surrounding the complications which attended 546 consecutive angiograms performed at this hospital between July 1952 and December 1956.

These arteriograms were performed by the resident staff of both the neurologic and neurosurgical services. Of the 546 arteriograms, 530 were performed by the percutaneous technic. In the 16 remaining cases the common carotid was exposed and cannulated either because of failure to puncture the artery by the percutaneous method or because of contemplated ligation of the artery. The injections were of 10 to 12 cc. of 35 per cent Diodrast,® except for 6 injections of 50 to 100 cc. of 70 per cent Urokon® via the antecubital vein.

These 546 procedures were performed in 483 patients, 275 of whom were male and 208 female. The youngest patient was three years old, the oldest eighty-five, 52 per cent of the patients being over fifty years of age. (Table I.)

A complication is defined, for the purposes of this study, as any objective detrimental alteration in the patient's well-being within the first twenty-four hours following arteriography. This arbitrary time limit was chosen in an attempt to eliminate those changes which might have appeared even if the arteriogram had not been obtained. A total of 109 complications occurred

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in this series. Over 90 per cent were manifested during or just after the procedure. These complications occurred in eighty-six patients (17 per cent), giving an over-all complication rate of 22 per cent in relation to the total number of patients or 19 per cent of the total number of arteriograms.

TABLE II
COMPLICATIONS OF ARTERIOGRAPHY

Complications	Total	Transient	Permanent
Non-fatal			
Progression of neurologic signs including:	43	30	13
Aphasia	6	4	2
Hemiparesis or partial hemisensory syndrome	9	6	3
Hemiplegia or complete hemisensory syndrome	7	3	4
Stupor	14	8	6
Convulsions, focal or general	6	6	0
Cavernous sinus thrombosis (partial)	1	1	0
Ipsilateral blindness	1	1	0
Meningeal reaction	1	1	0
Carotid sheath hematoma	1	0	1
Catatonic behavior	1	1	0
Quadriplegia	1	1	0
Nuchal hematomas, dysphagia or sore throat	37	37	0
Hemorrhage in fundi	3	3	0
Allergic reaction	6	6	0
Acute respiratory distress	12	12	0
Shock	7	7	0
Syncope while cannulating artery	1	1	0
Retropharyngeal hematoma	1	1	0
Fatal			
Immediate	0	..	..
Delayed:			
Directly related to arteriography	1	..	..
Questionably related to arteriography	7	..	..

Types of Complication. In Table II will be found a list of the complications encountered and their duration. This grouping, it will be noted, makes the number of complications appear greater since, for example, the group "progression of neurologic signs" also includes such complications as hemiparesis, aphasia and stupor.

All the patients were tested with 1 cc. of Diodrast prior to its use. Only one showed sensitivity, although there were six allergic reactions. These reactions were easily controlled with Benadryl.® The carotid sheath hematoma was found at necropsy.

Severity and Duration of Complications. The relationship between these factors is shown in Table III. A serious complication is considered as one which endangers life or leads to major neurologic sequellae. A transient complication is defined as one lasting less than six hours. Of the 109 complications in this series, forty-four were innocuous and transient, fifty-one were serious but transient and fourteen were permanent. Eight of the latter occurred in patients who subsequently died. No relationship was found between the severity of a given complication at its onset and its eventual outcome in regard to persistence.

TABLE III
DURATION AND SEVERITY OF COMPLICATIONS

Type of Complication	Total No. of Complications	No. of Patients with Complications
Transient	95 (87%)	75 (15%)
Innocuous	44 (40%)	41 (8.5%)
Serious	51 (47%)	34 (6.6%)
Permanent, non-fatal	6 (4%)	4 (0.8%)
Deaths	.....	8 (1.6%)*
Immediate	.....	0
Delayed, directly related to arteriography	.....	1 (0.2%)
Questionably related to arteriography	.....	7 (1.4%)

* These eight patients suffered nine serious complications, eight of which were classified as permanent.

The rate of permanent non-fatal complications was 0.8 per cent in this series. To attribute these complications solely to the effects of arteriography may be unjustified. Therefore the histories of the four patients experiencing non-fatal permanent complications are presented:

CASE I. I. T., a sixty-two year old woman, was aphasic, hemiparetic, lethargic, and had bloody spinal fluid on admission. At the time of arteriography she was stuporous and showed progression of neurologic signs. Just after a single injection of Diodrast there was a slight convulsion and the paresis became a hemiplegia. Three hours after the procedure, when the patient was less stuporous, a right homonymous hemianopia was demonstrated. This sign was equivocal at the time of admission. Three weeks after the arteriogram a third nerve palsy suddenly appeared and persisted. Eight weeks after arteriography the patient could walk with assistance but aphasia and visual defect persisted. Thirteen weeks after the first arteriogram a second was attempted to demonstrate a suspected aneurysm. This procedure was performed with 50 cc. of 70 per cent Urokon injected into the right antecubital vein while the patient was under amobarbital anesthesia. Immediatedly following the injection the patient had a brief generalized convul-

sion followed by a recurrence of the right hemiplegia. Within twenty-four hours the patient's condition had returned to that just prior to the second arteriogram.

CASE II. N. C., a fifty-eight year old man, with a blood pressure between 128/94 and 152/100 mm. Hg, was admitted to the hospital because of pain, stiffness and numbness of the right upper limb. One year before admission weakness and numbness of this member first appeared. These symptoms gradually subsided over the next seven months. In the three months prior to admission the symptoms gradually returned. At the time of admission these symptoms were fully developed but fluctuated somewhat in intensity. Aside from varicosities of both lower limbs and minimal arteriovenous nicking of the retinal vessels there were no abnormalities on general physical examination. Neurological examination showed mild weakness, slight dystaxia and minimal sensory defect of the right upper limb, these signs being more marked distally. The spinal fluid pressure and contents were normal. At the time of arteriography the patient was conscious. Three injections of 12 cc. of Diodrast were given into the left common carotid artery. With the third injection only the external carotid circulation was filled. The patient was returned to the ward alert, without complaints and was able to move all extremities. Nineteen hours after the arteriogram he was lethargic, had a global aphasia, a right visual field defect and a right hemiparesis. The lethargy improved but the other defects persisted.

CASE III. M. S., a forty year old woman, with a blood pressure of 120/70 mm. Hg, was admitted because of a slight right hemiparesis. One and a half years before, a right radical mastectomy was performed because of carcinoma of the breast. Prior to arteriography the patient was conscious and there was a minimal continuous increase in the signs of the right hemiparesis. Two injections (10 cc. each) of Diodrast were given into the left common carotid artery. The resulting arteriogram appeared normal. After the second injection, a gross right hemiparesis appeared and increased in severity until the time of operation three days after arteriography. A metastatic carcinoma of the left parietal region was demonstrated surgically.

CASE IV. R. W., a fifty-four year old woman, with a blood pressure of 190/90 mm. Hg, was admitted because of sudden onset of lethargy and a left hemiparesis. For twenty-eight years albuminuria had been noted. For six months hypertension was known to be present. Six days prior to admission a cataract was removed from the right eye. At the time of admission the patient was lethargic and had a left hemiparesis. Her spinal fluid was bloody, xanthochromic and under 320 mm. H_2O pressure. The course was progressively downhill. At the time of arteriography all signs and symptoms were rapidly increasing in severity. Immediately following arteriography, the patient was unchanged. Three hours later she became stuporous. Four hours after that her level of consciousness was once again at the prearteriographic state. Then consciousness gradually decreased. Within two hours she was comatose. This was twelve hours after the arteriogram, at which time an intracerebral hematoma, demonstrated by the arteriogram, was surgically evacuated. Postoperatively, her condition improved.

TABLE IV
COMPLICATIONS AND STATES OF CONSCIOUSNESS

State of Consciousness	Patients		Deaths Possibly Related to Arteriography
	Without Complications	With Complications*	
Conscious	319	56 (17%)	0
Obtunded	54	25 (45%)	6
Comatose	15	7 (47%)	1

* This includes the one patient whose death was directly attributable to the procedure.

In this series there were eight deaths, only one of which appeared to be directly related to arteriography. This death occurred in a patient with a background of treated syphilis who was being examined for a brain tumor. Six hours after the third injection of 12 cc. of Diodrast into the right common carotid artery, a complete left hemiplegia and hyperthermia developed. The subsequent course was downhill and death occurred on the second day after arteriography. Postmortem examination showed acute diffuse softening of the right cerebral hemisphere. No evidence of thrombosis or other pathologic conditions were observed nor were any structural abnormalities demonstrated to explain the acute softening and edema. In the other seven deaths the causal relationship between the arteriogram and the death is less clear. These patients died in nine to seventy-two hours after the procedure. The shortest interval was in a patient who was stuporous and had rapid progression of signs secondary to massive subarachnoid bleeding of undetermined etiology. There was no immediate untoward reaction. The arteriogram demonstrated a mass which proved to be an intracerebral hematoma. Five hours after its evacuation the number of retinal hemorrhages increased and eight hours after surgery the patient died. A second delayed death, occurred in a young man who was in coma and shock at

TABLE V
COMPLICATIONS AND RATE OF PROGRESSION OF ILLNESS

Status	Total No. of Patients	No. of Patients without Complications	No. of Patients with Complications			
			Innocuous, Transient	Serious, Transient	Permanent	Deaths
Stable	379	339 (89%)	27 (7%)	11 (3%)	2 (0.5%)	0
Slow progression	73	43 (59%)	11 (15%)	18 (25%)	0	1 (1.3%)
Rapid progression	31	15 (48%)	3 (9.7%)	5 (16%)	1 (3.2%)	7 (22.6%)

the time of arteriography which was performed with the hope of demonstrating a tuberculoma of the cerebrum. A third delayed death occurred twenty-six hours after arteriography was performed in an attempt to demonstrate an intracerebral hematoma in a patient who had suffered a subarachnoid hemorrhage. An aneurysm was demonstrated. During the procedure the patient, who prior to arteriography was going downhill rapidly and was semistuporous, passed into shock and showed signs of decerebrate rigidity. Just after arteriography the spinal fluid was found once more to be grossly bloody. Autopsy revealed rupture of the aneurysm through the cerebrum into the anterior tip of the temporal horn. A fourth delayed death occurred in a seventy-three year old woman. She had a background of chronic mental deterioration and at least one cerebrovascular accident. She was being investigated for a subdural hematoma succeeding trauma to the head and subsequent disturbance in consciousness. Following a second injection of 8 cc. of contrast medium which failed to fill the middle cerebral artery but did fill both anterior cerebral arteries, the patient suddenly became unconscious and convulsed. The fundi ipsilateral to the injection showed distinct narrowing of the vessels at this time. The ipsilateral pupil failed to react directly to light but did react consensually. Within a half hour the direct light reflex returned and the retinal blood vessel spasm was no longer observable. However coma and seizures continued; death ensued about three and a half days after the arteriogram. The remaining three patients had brain tumors and rapid progression of signs and symptoms. At the time of arteriography they were stuporous. Two of these patients died subsequent to surgery which was performed shortly after arteriography.

State of Consciousness and Complications. The relationship between the state of consciousness at the time of arteriography and the occurrence of complications will be seen in Table IV. The rate of complications in patients with depressed consciousness was about three times that in the fully conscious group. Serious complications also occurred twice as frequently in the group with depressed consciousness. This table lists separately the seven deaths questionably attributable to arteriography. The one death probably related to the procedure is included with the complications. The addition of the seven cases possibly related to arteriography makes the rate of total complications in patients with depressed consciousness 56 per cent.

TABLE VI
COMPLICATIONS AND NUMBER OF INJECTIONS

No. of Injections	No. of Patients	Complications	
		Total	Serious
0	8	3	1
1	66	24	15
2	329	38	28
3	72	17	8
4	8	4	1

Progression of Neurologic Signs and Complications. The relationship of the rate of downhill progression of the neurologic status and the occurrence of complications is expressed in Table V. A stable status is defined as one in which there was no change in the clinical signs or symptoms prior to the arteriogram. Such analysis shows that whereas 11 per cent of the patients with a stable neurologic status suffered a complication, 44 per

TABLE VII
COMPLICATIONS AND ETIOLOGY OF DISEASE OF CENTRAL NERVOUS SYSTEM

Disease	No. of Patients	No. of Patients with Complications			
		Total	Serious	Permanent	Death
Etiology demonstrated:					
Brain tumor*	192	32	15	1	3
Aneurysm	33	8	5	..	1
Vascular anomaly	15	..	..	..	..
Encephalopathy, diffuse, secondary to vascular disease	21	3	..	..	..
Hematoma, intracerebral	13	4	4	..	..
Hematoma, subdural	7	1	..	..	..
Thrombosis, internal carotid or branches	13	1	..	..	..
Carcinomatosis of meninges	1	1	..	..	..
Degenerative encephalopathy	12	4	..	..	..
Abscess	2	..	..	..	..
Acute cerebral malacia	2	2	..	..	1
Traumatic encephalopathy	6	2	..	..	..
Miscellaneous	9	1	..	..	1
Subtotal	326	59	24	1	6
Etiology not demonstrated	157	27	10	2	2
Total	483	86	34	3	8

* Three were also hypertensive.

TABLE VIII
COMPLICATIONS AND AGE

Age Groups (yr.)	No. of Patients	Complications	
		Total	Serious
0–10	8	.....	.....
11–20	15	4 (26%)	1
21–30	32	6 (18%)	3 (9%)
31–40	54	15 (28%)	5 (9%)
41–50	120	11 (9%)	7 (6%)
51–60	152	34 (22%)	21 (13%)
61–70	78	15 (20%)	6 (8%)
71–80	22	2 (9%)	1
81–90	2	2	.....

cent of those with increasing neurologic signs or symptoms did so. What is even more striking is that 87 per cent of the deaths and 67 per cent of the serious complications occurred in patients whose neurologic state showed rapidly progressive deterioration.

Number of Injections and Complications. No clear relationship was found between the incidence of complications or their severity and the number of injections of contrast medium. (Table VI.)

Nosologic Classification of Complications. Table VII indicates the relationship between the etiology of the disease of the central nervous system and the occurrence of complications. The value of such an analysis in this series is limited since the diagnosis was proved by surgery, autopsy or arteriography in only about two-thirds of the cases.

Age and Complications. The relationship between the age of the patient and the occurrence of complications is demonstrated in Table VIII. The total complication rates for each decade do not differ significantly. No complications were encountered below the age of eleven. The rate of serious complications also bears no significant relationship to age. The greatest number of complications occurred in the patients in the sixth decade, but this was the group in which most of the arteriograms were performed.

Vascular Status and Complications. The relationship between vascular status and complications is shown in Table IX. Patients with systemic arteriosclerosis and/or hypertension and those without known systemic vascular disease had the same rates of complication. It should be emphasized that 79 per cent of patients with hypertension did not suffer any

TABLE IX
COMPLICATIONS AND VASCULAR STATUS

Vascular Status	No. of Patients	No. of Patients with Complications			
		Total	Serious	Permanent	Death
No known systemic vascular disease	344	55	24	1	4
Systemic hypertension	86	18	9	1	1
Systemic arteriosclerosis	59	12	1	1	2
Shock	1	1	..	..	1

complication. Of the complications in the hypertensive group, about three-fourths fell into the transient-serious category.

Anesthesia and Complications. Finally, the occurrence of complications was considered in relation to the type of anesthesia used during the procedure. (Table x.) It will be seen that the incidence of complications was almost three times greater in patients receiving intravenous amobarbital or pentobarbital than in those receiving only local anesthesia with intramuscular premedication of atropine sulfate and phenobarbital sodium, and that the rate of serious complications was still greater in the former group. In this series, inhalation anesthesia was used in young children. Intravenous barbiturate was used in adults too agitated or apprehensive to undergo the procedure with local anesthesia.

COMMENTS

The nature of the population studied needs consideration before any conclusion may be drawn from these data. All of the arteriograms performed within the stated period were included in this study. In this sense the sample was non-selective. However, there were factors which tended to bias this sample. The fact that the Hospital does not maintain an ambulance service tends to exclude cases of trauma to the head. Cerebral vascular accidents occurring in the course of arteriosclerotic or hypertensive vascular disease were not investigated arteriographically unless brought to the neurologic service because of signs suggesting aneurysm, intracerebral or subdural hematoma or neoplasm. In cases of bleeding aneurysm there was a tendency to delay arteriography until the patient began to recover. When possible, lightening of the stupor or coma was awaited. However, arteriography was performed in the presence of active cardiovascular disease, increased intracranial pressure, progression of neurologic signs or depressed states of consciousness if, on clinical grounds, it was considered that data helpful to the patient could be obtained. In view of these factors this series must be considered partially selective and therefore not subject to the analysis applicable to random samples. Nevertheless the data serve to emphasize certain points.

TABLE X
COMPLICATIONS AND ANESTHESIA

Type of Anesthesia	No. of Patients	Complications	
		Total	Serious
Intravenous barbiturates (amobarbital, pentobarbital)	46	18 (40%)	13 (28%)*
Inhalation	5	1	0
Local, after premedication with phenobarbital and atropine	432	68 (16%)	32 (7%)†

* Including one death probably related to arteriography.
† Including seven deaths possibly related to arteriography.

Strict comparison with the incidence of complications in other studies on this subject is difficult because of the many variables involved, differences in definition of a complication, and differences in the populations studied as a result of stated and hidden selective factors. This last point is of special importance since few articles on this subject have stressed the selective nature of the samples studied. Even less frequently analyzed has been the medical status of the population which did not suffer a complication from arteriography. Such comparison as is possible among the reported series may however be fruitful if carried out by considering the relationship between the incidence of complications on the one hand, and on the other the state

of consciousness, the presence of blood in the cerebrospinal fluid, the presence of hypertensive arteriosclerotic disease, the etiology of the neurologic disease and the use of general anesthesia.

In our series, the incidence of complications was about twice as great in patients with impaired consciousness at the time of arteriography as in conscious patients. (Table IV.) The rate of serious complications was also twice as high in the former group. A higher incidence of complications in stuporous, comatose and moribund patients has been previously reported [*17,18*]. The explanation for this phenomenon is not known.

In this series nine of twenty-one patients with blood in the spinal fluid suffered complications. One patient had urticaria, nuchal hematoma developed in four, one had transient unilateral blindness secondary to retinal arterial spasm. A seventh patient, obtunded at the time of arteriography, passed into coma three hours after the procedure which demonstrated an intracerebral hematoma subsequently removed surgically. An eighth patient had had two previous subarachnoid hemorrhages. Bilateral papilledema subsequently developed and he passed into coma in a matter of hours. An emergency arteriogram was performed with no immediate untoward effect. An intracerebral hematoma was then evacuated. Six hours later the number of retinal hemorrhages increased. Eight hours after operation the patient died. A ninth patient was going rapidly downhill and passed into shock and decerebrate rigidity just after the arteriogram. Postmortem examination revealed a ruptured aneurysm with intracerebral and intraventricular hemorrhagic extensions.

It is difficult to discern any direct relationship between the presence of blood in the spinal fluid and the occurrence of a complication in these cases. In the ninth case it is possible that the arteriogram produced transient ischemia following which the aneurysm bled further and extended intracerebrally. However, such an extension is often seen without arteriography. The possibility of a relationship between an arteriographic complication and blood in the spinal fluid must also be assessed in light of the fact that twelve patients with blood in the spinal fluid had uncomplicated arteriograms, while forty-five patients with non-bloody spinal fluid experienced a serious complication.

In this series, as noted in Table VII, there were thirty-three aneurysms demonstrated by arteriography. In eight of these cases there were complications. These included one nuchal hematoma, two retropharyngeal hematomas, one increase in degree of a third nerve palsy, two cases of increased degree of hemiparesis, one episode of laryngospasm, and one possible death. This last case was described as the ninth case in the preceding paragraph. In this series only one patient with proved aneurysm had an arteriogram when the spinal fluid was bloody. At this time papilledema also was present. This patient did not suffer a complication.

The incidence of complications in the presence of intracerebral hematoma was higher than in other diseases in this series. There were thirteen such hematomas, four of which were attended by postarteriographic complications. Of the latter patients, the first was stuporous and had bloody, xanthochromic spinal fluid under increased pressure at the time of arteriography. Three hours after the procedure the patient passed into coma and two hours later the hematoma was successfully evacuated. The second case was complicated by transient blindness secondary to retinal arteriolar spasm. The third patient had a cerebral hemorrhage secondary to hypertensive disease. At the time of arteriography this patient was in stupor and showed progression of neurologic signs. There was no immediate postarteriographic change. Two hours after the procedure, the patient lapsed into coma. Emergency burr holes were performed without giving evidence of a subdural hematoma and forty-eight hours after admission the patient died. The diagnosis was made at postmortem examination. The fourth patient with proved pontine hemorrhage in the course of a malignant hypertension with labile blood pressure went into shock just after the arteriogram. The recovery from this complication was slow but uncomplicated. It is of interest that a patient with a bifrontal intracerebral hematoma demonstrated angiographically did not suffer any complication. Just prior to the procedure this patient was disoriented but not obtunded. These cases do not allow for any generalizations in regard to the apparently greater incidence of complications in the presence of an intracerebral hematoma.

This series included seven patients with subdural hematomas, in one of whom the arteriogram was attended by generalized urticaria immediately relieved by intravenous Benadryl.

Incidentally, this patient was comatose at the time of arteriography and it was later shown that the subdural hematoma was associated with carcinomatosis of the meninges. Of the six patients with subdural hematoma who did not suffer an arteriographic complication, four were very sick at the time of the procedure; one was obtunded, two were comatose, and one was lethargic. The absence of complications in this group of patients is interesting in view of a recent report on subdural hematomas in which it was stated that "air studies or arteriography are not well tolerated by the very sick patient, and bilateral temporal (and/or other) burr holes are safer and nearly always diagnostic" [*16*].

Our experience with acute vascular accidents thus seems to indicate that fresh blood in the spinal fluid, and the presence of intracranial aneurysms and intracranial hematomas are not contraindications for arteriography, which may be the best method for arriving at a rational course of management. A somewhat similar viewpoint was recently expressed by another investigator, Segelov [*22*] who concluded that acute bleeding even in the presence of shock is not a contraindication to arteriography if it may be expected to lead to a life-saving therapeutic regimen.

The consensus in the literature on arteriographic complications is that cerebrovascular disease, particularly insufficiency from any cause, is attended by a high rate of postarteriographic complication. Our data do not fully bear this out, as will be seen in Table IX. If we consider all the patients with evidence of vascular disease as a unit, the incidence of complications other than innocuous (e.g., nuchal hematomas, allergic reactions, laryngospasm) was 11 per cent. The incidence of complications for those without known vascular disease was 8 per cent. This difference does not appear to be significant. Similarly, the conclusion that either hypertension or arteriosclerosis* *per se* was a factor leading to complications in our series seems untenable since about 80 per cent of those with hypertension or arteriosclerosis did not suffer any complications at all. What may be significant is that 72 per cent of the complications in the hypertensive patients were serious although transient, whereas only 47 per cent of the complications in the entire group fell into this category. A consideration of the background as well as the circumstances surrounding these complications seems to indicate factors other than hypertension to be related to the occurrence of the complication. In the presence of hypertension serious arteriographic complications usually occurred in those patients who had other grave diseases, e.g., intracranial hematomas, marked depression of consciousness, or brain tumor. The one exception was patient N. C. (Case II), whose highest recorded blood pressure was 152/100 mm. Hg and who before arteriography had episodic weakness and numbness of the right upper extremity. After the arteriogram a permanent right hemiparesis, a right homonymous hemianopia and aphasia developed.

Even more instructive is patient A. E. This patient's hypertension and arteriosclerosis were known for at least ten years and attended by chronic renal disease. At the time of arteriography the blood pressure was 220/120 mm. Hg. Three arteriograms were obtained in this patient. The first was a right percutaneous carotid angiogram. Two injections failed to give enough evidence for a conclusive diagnosis of an intracranial mass. Because of progression of neurologic signs and the onset of stupor and papilledema, a second arteriogram was attempted by injecting 100 cc. of Urokon (70 per cent) into the right antecubital vein. This procedure also failed to provide a definite diagnosis. In view of further rapid progression a third arteriogram was performed, at which time the patient was restless and semistuporous. This procedure was a right percutaneous carotid arteriogram. After a third injection of 10 cc. of Diodrast there was a generalized convulsion, cyanosis, complete unresponsiveness, and the patient passed into shock. A half hour later the patient responded to verbal commands. Thereafter, the downhill progression was more rapid and renal shutdown occurred. The patient died two days later. Postmortem examination showed a glioblastoma multiforme.

Complications such as urticaria, laryngospasm and nuchal hematoma did not seem to be related to hypertension and so may be excluded in assessment of the role of this factor in arteriographic complications. Thus, for this series no causal relationship between hypertensive disease and arteriographic complication appears demonstrable.

The same type of analysis may be applied to the arteriosclerotic group. The results of such analysis failed to reveal any causal relationship

* Separation of the hypertensive and arteriosclerotic patients was made with the knowledge that the hypertensive patients have a high incidence of arteriosclerosis.

between cerebral arteriosclerosis and the occurrence of a postarteriographic complication. Indeed, three patients with marked cerebral arteriosclerosis demonstrated by autopsy did not suffer any complications.

It has been stated that intubation and intravenous barbiturates administered by an anesthetist reduce the risk of complication [*1*]. Our data, in contrast, show the incidence of complications to be 40 per cent with intravenous barbiturates and only 16 per cent with local anesthesia. Again, the circumstances leading to this higher rate with intravenous anesthesia demand scrutiny. In our series intravenous barbiturates were used because of inability to cooperate. Such behavior usually occurred in patients with severe neurological disease and depressed states of consciousness or an acute anxiety reaction.

The absence of any serious complication and the occurrence of three innocuous complications in patients below the age of nineteen is in agreement with the experience of others [*20,21*].

The mortality rate in this series was 0.2 per cent or 1.6 per cent, depending upon whether or not, as already discussed, one or eight deaths are to be attributed to the arteriographic procedure. In previously reported series (*op. cit.*) the mortality rate varied from 0 to 3 per cent.

The frequency and variety of complications reported in this series are of interest in another respect. A recent report of another series of angiograms performed in 400 patients concluded that no complications were encountered [*22*]. The technic used does not appear to be substantially different in the two series except that anesthesia was employed in over half of the patients in the latter series What does appear to account for the difference in the number of complications is the difference in the definition of a complication. Thus in the latter series the 204 nuchal hematomas were not considered complications, nor were three cases of laryngospasm, or seven cases of cutaneous rash. In this latter series no deaths or permanent sequellae occurred. This was attributed in part to the small volume of contrast agent (essentially the same volume as in the present series) and the surgical treatment of any large space-occupying lesion within twelve hours.

SUMMARY

Analysis of 109 complications occurring in 483 patients in whom 546 cerebral angiograms were obtained indicates two factors to be associated with the occurrence of serious complications: (1) depression of consciousness, (2) progression of neurologic signs.

In this series no relationship between the cardiovascular and hypertensive status of the patient and occurrence of a complication was demonstrable. One-fourth of the patients with aneurysms suffered a serious complication; no apparent cause for this high rate was found. Of the non-fatal complications 0.8 per cent were permanent. In only one case did death appear to be directly attributable to the procedure. In seven cases the relation of the procedure to the ultimate death of the patient was probably not causal.

The value of arteriography must be considered in view of the incidence and severity of such complications. In this series 80 per cent of the arteriograms gave diagnostically useful information. Therefore, in consideration of the low rate of significant morbidity and the low rate of mortality, it is our opinion that in selected cases cerebral arteriography provides diagnostic information which outweighs the risk of complication.

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Recurrent Nephrolithiasis Associated with an Unusual Tubular Defect and Hyperchloremic Acidosis*

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THE clinical and laboratory features of primary renal tubular acidosis originally reported by Butler et al. [*1*] and Albright et al. [*2,3*] have since been well documented [*4,12*]. The basic defect in this syndrome is construed as a failure of normal mechanisms of urine acidification. The urine is persistently alkaline or slightly acid despite a mild to moderate systemic acidosis. Renal conservation of inorganic cations is inefficient, and on restricted or even normal diets calcium is wasted in the urine. In some instances potassium depletion may ensue. Nephrocalcinosis and nephrolithiasis may stimulate early clinical recognition; generalized skeletal disease may occur in cases of long standing. Progressive renal damage and secondary pyelonephritis may ultimately lead to uremia.

In the process of routine screening of patients with recurrent nephrolithiasis for a metabolic defect we recently encountered a patient with hyperchloremic acidosis and a paradoxically high output of ammonia (30 to 60 mEq. per day) in the presence of a urinary pH ranging between 6.60 and 7.20. Normally the concentration of ammonium decreases with progressive alkalinization of the urine [*13*]. Aberrations from the normal inverse relationship between urine ammonium and pH have been observed in isolated instances of the Fanconi syndrome, in the recovery phase of tubular necrosis, in potassium depletion with and without hyperaldosteronism, after infusion of amino acids [*14,15*], and after the administration of ammonium chloride to patients with renal tubular acidosis [*16*]. A review of published cases of renal tubular acidosis reveals that in some patients the excretion of ammonia is not decreased in relation to the increased urine pH [*3–5,10,12,16*] but none exhibited the marked disparity observed in our patient. This is a report of the studies undertaken to outline more clearly the renal tubular defect and the mechanism of ammonia excretion in this patient.

MATERIAL AND METHODS

The procedures regularly employed in this department for prolonged metabolic balance studies have been previously described [*17*]. Urine was collected under oil and refrigerated immediately; toluene was used as a preservative. Chemical analyses of blood and urine were performed by standard methods [*18*]. Because of the variety of tests performed, the details of the protocol of each acute or chronic metabolic study will be described with the presentation of each experiment.

CASE REPORT

The patient was a thirty-three year old white man who had his first attack of renal colic at the age of twenty-seven in 1951. He passed at least thirty stones from 1951 to 1957. He underwent surgery three times: several calculi were removed from the left renal pelvis in August 1951 and May 1952, and from the right renal pelvis in March 1956. Prior to 1951 the patient was in perfect health and had had no symptoms suggestive of renal disease. There was no history of joint or bone disease. His intake of milk was not excessive, and he never took alkaline medications. It is of special interest that on each examination the urine pH was consistently above 6.0 from the time he passed his first stone; furthermore, several courses of mandelamine® therapy in combination with an acid-ash diet failed to influence the pH of his urine.

The patient's parents and three children gave no

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history of renal disease. Their blood electrolytes and x-ray films of the renal region were within normal limits. In all, the urine could acidify to a pH below 5.90, as measured in specimens taken at random.

Laboratory data revealed a urine pH of 6.60 to 7.20, albumin negative, glucose negative, sediment negative. The maximal and minimal specific gravities in concentration and dilution tests were 1.022 and 1.003 respectively. The glomerular filtration rate (inulin clearance) was 100 to 106 ml./minute, renal plasma flow (para-aminohippurate clearance) 561 to 731 ml./minute; phenolsulfonphthalein excretion 45 per cent in twenty minutes and 72 per cent in 120 minutes. The hemoglobin was 15.6 gm. per cent, leukocytes 5,900 per cu. mm. with a normal differential count. The blood urea nitrogen was 13 mg. per cent; creatinine 1.3 mg. per cent; uric acid 4.8 mg. per cent; sodium 142 mEq./L.; potassium 4.1 mEq./L.; chloride 110 mEq./L.; carbon dioxide content 20.2 mEq./L.; blood pH 7.30; calcium 10.6 mg. per cent; phosphorus 3.8 mg. per cent; alkaline phosphatase 2.9 Bodansky units. The renal stones were found to be composed of calcium and magnesium phosphate and carbonate.

In 1956 one small renal stone was found roentgenographically to be present in each renal pelvis. No nephrocalcinosis was evident. An intravenous pyelogram disclosed no mechanical obstruction in any part of the urinary tract. A bone survey revealed no demineralization, and no indication of osteomalacia.

SPECIAL STUDIES OF RENAL FUNCTION

The persistent elevation of the urinary pH above 6.60 indicates that the patient's renal mechanism for urine acidification was inadequate. Insufficient acid excretion resulted in a mild acidosis with a decreased plasma carbon dioxide content and hyperchloremia. Very early in the course of this study it was found that the daily excretion of ammonium was paradoxically high (30 to 60 mEq.) for the urine pH, which ranged between 6.60 and 7.20. It should be stressed that at the time of these determinations the urine cultures were sterile. Urinary titratable acidity (TA) varied between 8.5 and 16.4 mEq. per day, and bicarbonate excretion ranged from 9.8 to 24.1 mEq. per day. The glomerular function was normal. The normal para-aminohippurate clearance, phenolsulfonphthalein test, and absence of glycosuria and acetonuria indicated normal proximal tubular function. This was further substantiated by the absence of excessive amino-aciduria (342 to 427 mg./day) and a normal phosphorus clearance of 9.8 ml./minute, as measured in the fasting state during the forenoon [*19*].

Distal Tubular Regulation of Water. Since the concentration and acidification of the urine are usually considered specific distal tubular functions, it was considered of importance to determine the patient's ability to reabsorb water and his response to a sustained water load. The maximal range of urinary specific gravity on water deprivation and hydration was 1.022 to 1.003. The maximal tubular reabsorption of water free of solute ($T^c_mH_2O$) after three intravenous injections of 200 milliunits of pitressin® at hourly intervals during an osmotic diuresis induced with 1,000 ml. of 10 per cent mannitol was 5.2 ml./minute. Urine osmolality after overnight dehydration was 905 mOsm./L. with a serum osmolality of 282 mOsm./L. These values are within the range observed by us and by Epstein et al. [*20*] in normal persons on previously unrestricted fluid intake. The response to a water load of 500 ml. every thirty minutes for three hours was also comparable with the results obtained in normal subjects by Welt and Nelson [*21*]. The urine flow rose to 17.3 ml./minute, which represents 17 per cent of the simultaneously determined glomerular filtration rate. The U/P ratio for creatinine reached a minimum of 6.6. These data indicate that the patient's tubular defect did not involve the site and mechanism for urine dilution and concentration. He was therefore challenged with various stimuli which normally increase urinary acid excretion.

Ammonium Chloride Acidosis. The patient was given a constant liquid diet calculated to be neutral in ash [*22*]. After a five-day period of equilibration he received ammonium chloride in the form of non-enteric coated tablets, 2 gm. every six hours for four days (150 mEq./day). This aggravated his metabolic acidosis, as illustrated by a drop of the blood pH to 7.20 and of the serum bicarbonate to 14.1 mEq./L. (Table 1.) Serum sodium, potassium, calcium and phosphorus concentrations remained unchanged. The chloride level rose from 108 to 115 mEq./L. The effect on urine acidification was subnormal: the urine pH fell from 6.63 to 6.20. The increased excretion of ammonia (Fig. 1) and of titratable acidity (Fig. 2) was inferior to the response to the same acid load observed in normal subjects studied at this department [*23*]. Thus the patient "covered" a larger proportion of the excess anion load with inorganic cation, suggesting a defect in hydrogen ion production or excretion. It should be noted in

TABLE 1

RENAL RESPONSE TO PROLONGED AMMONIUM CHLORIDE ADMINISTRATION

Data	Plasma			Urine								
	pH	HCO_3 (mEq./L.)	Cl (mEq./L.)	pH	HCO_3	NH_3	TA	Na	K	Ca	Cl	P (gm./24 hr.)
					(mEq./24 hr.)							
Control period. Days of NH_4Cl ingestion:	7.31	20.2	108	6.63	9.77	30.7	16.4	103	90	11	130	1.15
Day 1.....	....	....	...	6.61	9.69	30.7	19.1	223	115	17	258	1.08
Day 2.....	....	....	...	6.35	7.10	43.1	26.3	170	163	16	290	1.33
Day 3.....	....	....	...	6.27	7.10	55.2	29.1	197	180	21	315	1.46
Day 4.....	7.20	14.1	115	6.20	4.38	61.4	31.1	104	158	17	227	1.53

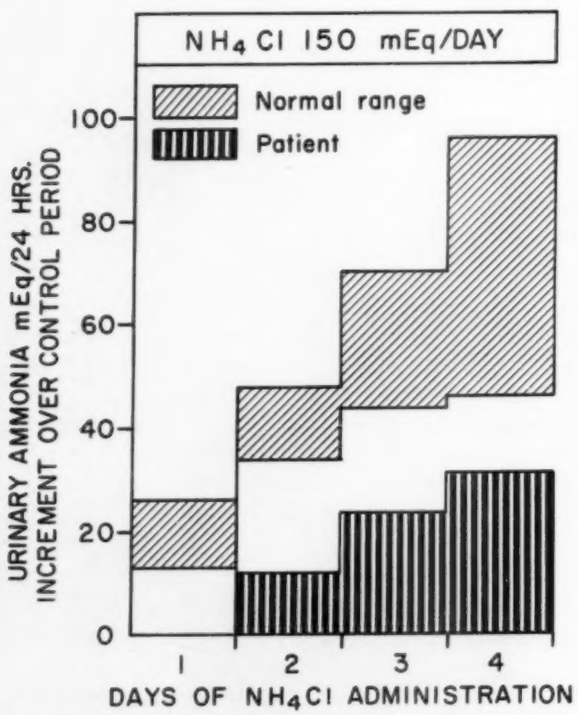

FIG. 1. Response of urinary ammonium to NH_4Cl administration.

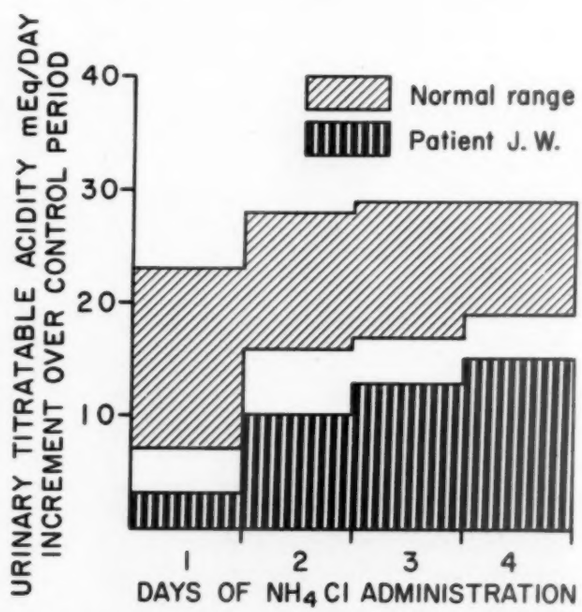

FIG. 2. Response of urinary titratable acidity to NH_4Cl administration.

Table 1 that the quantity of urinary ammonium excreted on the last day of ammonium chloride administration (61.4 mEq.), although low for the degree and duration of extracellular acidosis, was paradoxically high for a urine pH of 6.20. It is also remarkable that on the same day the urine still contained 4.4 mEq. of bicarbonate. That bicarbonate should continue to be excreted despite the reduced serum bicarbonate levels suggests a major alteration of bicarbonate threshold and is compatible with the thesis that a defect in bicarbonate reabsorption plays an important role in the development of metabolic acidosis in this syndrome.

Respiratory Acidosis. Ten per cent carbon dioxide in 90 per cent oxygen was administered to the patient in an oxygen tent. The gas mixture was introduced at a rate of 14 L. per minute for twenty-five minutes. The tent was not airtight, and the concentration of carbon dioxide inhaled probably never reached 10 per cent. It

TABLE IIA*

RENAL RESPONSE TO RESPIRATORY ACIDOSIS

Total Elapsed Time (min.)	Plasma		Urine									
	pH	HCO_3 (mEq./L.)	pH	HCO_3	NH_3	TA	Na	K	Ca	Cl	P (μg./min.)	Flow (ml./min.)
				(μEq./min.)								
0–55	7.31	20.6	6.79	19.2	25.8	6.2	155	79	6	30.9	301	4.7
Inhalation of 10% CO_2 and 90% O_2 Between 59–85 Minutes												
55–86	7.00	20.3	6.57	40.3	48.0	18.4	175	65	12	55.8	476	12.2
86–117	(lost)	....	6.55	39.8	51.2	18.5	184	72	11	72.2	587	13.2
117–146	7.30	20.2	6.50	39.8	52.2	19.2	138	62	8	65.3	527	13.4

* Blood for determination of pH and HCO_3 was collected at the end of the single study periods.

TABLE IIB

RENAL FILTRATION, REABSORPTION AND EXCRETION OF BICARBONATE DURING RESPIRATORY ACIDOSIS

Total Elapsed Time (min.)	Data	Gas Breathed	Urine Flow (ml./min.)	GFR* (ml./min.)	Plasma			HCO_3			
					pH	HCO_3 (mEq./L.)	pCO_2 (mm. Hg)	Filtered (mEq./min.)	Excreted (mEq./min.)	Reabsorbed (mEq./min.)	Filtrate (mEq./min.)
0–55	Control	Room air	4.7	107	7.31	20.6	50	2.19	0.019	2.17	20.28
55–86	Stimulus	10% CO_2	12.2	122	7.00	20.3	97	2.47	0.040	2.43	20.00
117–146	Recovery	Room air	13.2	100	7.30	20.2	50	2.02	0.040	1.98	19.90

* Glomerular filtration rate.

was of sufficient concentration, however, to induce a severe acidosis with a drop of blood pH from 7.31 to 7.00. (Table IIA.) The urine pH fell from 6.79 to 6.50, and the excretion of ammonia, titratable acidity and phosphate rose moderately. The net rise in urinary hydrogen ion excretion above the control period ($\Delta U_{NH_4} + \Delta U_{TA} - \Delta U_{HCO_3}$) was only 13 μEq./minute, which is approximately one-sixth of the response of normal subjects exposed to a similar stimulus [*24*]. Potassium excretion, which normally falls during respiratory acidosis, was not significantly altered. The relatively low excretion of bicarbonate during the control period was probably related to the low urine flow. The reabsorption of bicarbonate (Table IIB), which normally is a linear function of plasma carbon dioxide tension (pCO_2) [*25*], remained unchanged despite a rise in pCO_2 from 50 to 97 mm. Hg. The failure in bicarbonate reabsorption was the major cause of the acute fall in blood pH. As in normal subjects [*24*], the renal response to respiratory acidosis persisted for at least one hour after cessation of carbon dioxide inhalation.

Infusion of a Buffered Phosphate Solution. The infusion of a solution of sodium phosphate with a pH of 7.40 is known to induce acidification of the urine [*4,5,13*]. A solution containing 43.12 gm. $Na_2HPO_4.2H_2O$ and 11.48 gm. $NaH_2PO_4.H_2O$ in 1,000 ml. of distilled water with a pH of 7.40 was administered over a period of five hours. The rate of infusion was gradually increased from 1.0 ml. per minute at the onset to 3.0 ml. per minute at the end of the infusion. The results of this study are presented in Table III. The urine pH fell only from 6.89 to 6.54, despite a rise in titratable acidity from 6.6 to 94.9 μEq./minute. There was no significant change in ammonium excretion. While the

TABLE III*

RENAL RESPONSE TO THE INFUSION OF A BUFFERED PHOSPHATE SOLUTION

Total Elapsed Time (min.)	Plasma			Urine									
	pH	HCO_3 (mEq./L.)	P (mg. %)	pH	HCO_3	NH_3	TA	Na	K	Ca	Cl	P (μg./min.)	Flow (ml./min.)
					(μEq./min.)								
0–33	7.37	19.4	3.49	6.89	57.3	57	6.6	244	37	21.9	...	175	14.8
Infusion of Buffered Phosphate Solution from 33 to 304 Minutes													
33–63	....	....	.....	6.90	67.6	71	7.0	297	46	22.1	223	221	17.3
63–94	....	....	4.50	6.81	62.0	62	11.9	290	39	18.4	206	680	15.2
94–126	....	....	6.13	6.75	53.0	68	30.0	309	41	16.0	164	2503	13.2
126–160	....	....	7.43	6.68	42.3	47	49.4	332	52	12.4	129	3651	10.3
160–185	7.35	19.6	10.48	6.58	43.8	65	75.2	329	57	11.1	92	4829	11.5
Diamox, 750 mg., Orally at 185 Minutes													
185–214	....	....	11.42	6.54	50.8	66	94.9	404	54	12.3	83	6062	13.6
214–244	....	....	14.11	6.78	92.4	59	84.2	548	81	12.4	121	7583	14.6
244–274	7.35	19.4	15.67	6.89	103.0	50	81.9	661	110	11.7	134	9943	12.1
274–304	7.33	18.7	17.25	6.89	105.0	50	91.7	586	94	13.8	85	9746	14.3

* The blood for pH, HCO_3 and P determination was collected at the end of the pertinent study periods.

TABLE IV

RENAL RESPONSE TO DIAMOX

Total Elapsed Time (min.)	pH	HCO_3	NH_3	TA	Na	K	Flow (ml./min.)
		(μEq./min.)					
0–60	6.96	54	39.3	8.3	320	65	8.5
Diamox 1,000 mg. Orally at 60 Minutes							
60–120	7.60	271	14.3	...	537	86	13.9
120–180	7.68	389	8.3	...	760	112	9.4
180–240	7.66	290	7.1	...	568	92	7.6
240–300	7.69	253	5.9	...	475	85	6.4
300–360	7.66	202	4.7	...	372	84	3.3

infusion of phosphate continued, the patient was given 750 mg. of diamox® orally. This increased the bicarbonate excretion, and the urine pH returned to the baseline value of 6.89. The rise in titratable acidity was arrested, and ammonium excretion dropped. The exact mechanism of urinary acidification induced by the infusion of a buffered phosphate solution is not known, although undoubtedly it is related to the increased availability of urinary buffer. The excessive hydrogen ion excretion is essentially the result of the conversion of disodium to monosodium phosphate by cation exchange at the tubular level. The antagonistic effect of diamox on the production of titratable acidity and ammonium implies that both mechanisms of acid excretion depend on carbonic anhydrase activity as a source of hydrogen ions. The rate of bicarbonate reabsorption in this study rose only slightly before administration of diamox, suggesting that this mechanism of urinary acidification contributed very little to the drop in urine pH during phosphate infusion.

Effect of Diamox. Since the patient's urine could not acidify normally under the stimulus of various acute and chronic states of acidosis, it was considered of interest to test the adaptive function of the patient's tubules to stimuli which are known to induce the excretion of a more alkaline urine. The response to 1,000 mg. of diamox administered orally was essentially normal. (Table IV.) The urine pH rose from 6.96 to 7.69 with a concomitant acceleration of bicarbonate and sodium excretion. Titratable acidity and ammonium fell to very low levels. This response indicates that the patient must possess at least a certain degree of carbonic anhydrase activity which can be depressed by an inhibitor. This test also excludes the possible role of bacterial contamination in accounting

TABLE V*

RENAL RESPONSE TO RAPID INFUSION OF $NAHCO_3$

Total Elapsed Time (min.)	Plasma		Urine								
	pH	HCO_3 (mEq./L.)	pH	HCO_3	NH_3	TA	Na	K	Cl	P (μg./min.)	Flow (ml./min.)
				(μEq./min.)							
0–25	7.34	21.1	6.77	17.1	29.9	8.8	103	68	16.7	389	5.0
25–67	....	....	6.60	30.8	22.4	9.0	83	59	36.4	349	7.7
180 mEq. $NaHCO_3$ Intravenously from 72 to 87 Minutes											
67–92	7.46	26.5	7.29	215.2	20.8	1.6	451	111	51.9	316	13.8
91–122	....	....	6.95	70.2	17.8	8.0	181	98	41.8	384	9.0
122–154	....	....	6.65	34.6	18.0	9.6	87	69	22.2	324	7.0
154–202	....	....	6.66	26.5	16.4	8.2	58	54	19.5	320	7.0

* Blood for determination of pH and HCO_3 was collected at the end of the single study periods.

for the elevated urine ammonia, because one would not expect any inhibiting action of diamox on bacterial enzymes capable of producing ammonia. Kaye [*26*] has examined the response to diamox in three patients with hyperchloremic acidosis. Only the patient with the least degree of acidosis (HCO_3: 20.1 mEq./L.) responded; the other two with serum bicarbonate levels of 14.0 and 14.8 mEq./L. failed to respond. Correction of the acidosis with sodium citrate partially restored the responsiveness to diamox. Our patient resembles the first case of Kaye in this respect. It was suggested that the response to diamox was perhaps limited by the degree of acidosis [*27*] rather than by the severity of tubular damage.

Infusion of Sodium Bicarbonate. The patient was given 180 mEq. of sodium bicarbonate (200 ml. of a 7.5 per cent solution) intravenously over a period of fifteen minutes. The renal response (Table v) was similar to the one observed in normal subjects by Singer et al. [*28*]. The urine pH rose from 6.77 to 7.29 with a marked increase of bicarbonate and sodium excretion. The depression of urinary ammonia and titratable acidity was less pronounced. Potassium excretion was exaggerated.

Citrate Metabolism. The plasma citric acid level was 8.15 mM./L., a value which is at the lower limit of normal. The excretion of citrate was 22.8 mg./twenty-four hours, which is only a fraction of the usual normal values (200 to 1,000 mg.) [*29*]. Citrate is rapidly utilized by bacteria in the urine [*30*], but the finding of negative cultures and the immediate refrigeration of each urine specimen make it unlikely that bacterial contamination influenced the findings. We have found only one report of citrate excretion in tubular acidosis: Harrison and Harrison [*31*] refer to an infant with hyperchloremic tubular acidosis with a "urine lacking in citrate even after large doses of sodium bicarbonate and Vitamin D." Unfortunately, we did not test the ability of our patient to increase citric acid excretion under these stimuli. It is of special interest in this connection that diamox depresses citrate excretion [*31*] and that nephrolithiasis has been reported in man [*32,33*] and rats [*31*] after prolonged administration of this carbonic anhydrase inhibitor. The theory that a decrease in urinary citric acid may lead to precipitation of calcium salts appears attractive.

Calcium Excretion. The daily urinary loss of calcium ranged between 302 and 344 mg. during a seven-day period of dietary calcium restriction to 300 mg./day. In a subsequent period of nine days on a 2,000 mg. calcium diet, the urine calcium varied between 226 and 352 mg./day. The change in calcium intake had very little effect on calcium excretion. At a low intake the patient was in negative balance and at a high intake he was probably in positive balance. The absence of bone disease indicates that the patient's intake of calcium must have been sufficient to prevent a prolonged negative balance.

The effect of sodium citrate therapy is illus-

TABLE VI

EFFECT OF SODIUM CITRATE THERAPY ON SYSTEMIC ACIDOSIS AND URINARY CALCIUM EXCRETION*

Data	Plasma				Urine					
	pH	HCO_3	Cl	Na	pH	Ca (mg./24 hr.)	HCO_3	NH_3	TA	Na
		(mEq./L.)					(mEq./24 hr.)			
Control period:										
Day 1	....	....	...	...	....	362	....	..	....	.....
Day 2	....	....	...	...	....	298	....	..	....	86.4
Day 3	....	....	...	...	6.65	277	....	60	11.9	86.9
Day 4	7.27	19.4	114	142	6.67	332	11.8	52	11.9	81.9
Period of sodium citrate therapy:										
Day 5	....	....	...	...	....	193	....	..	....	114
Day 6	....	....	...	...	....	171	....	..	....	120
Day 7	....	....	...	...	....	212	....	..	....	140
Day 8	....	....	...	...	....	172	....	..	....	130
Day 9	....	....	...	...	7.25	179	34.8	30	1.5	143
Day 10	7.34	27.6	102	150	7.33	175	41.2	35	0.7	148

* 20 ml. of an 8.7 per cent sodium citrate solution administered five times daily.

trated in Table VI. During this study the patient was taking a constant liquid diet containing 375 mg. of calcium, 800 mg. of phosphorus, and 100 mEq. of sodium per day. Even in the absence of stool electrolyte determinations it is probable that the patient was in negative calcium balance during the preliminary control period, because the urinary calcium closely approached the intake, and there is always an obligatory amount of fecal calcium. Sodium citrate effectively corrected the metabolic acidosis and depressed urinary calcium excretion. This response to alkali therapy has been considered by Albright [*3*] to be a prerequisite for the diagnosis of hyperchloremic tubular acidosis. The rationale of this therapy is based on the assumption that calcium is excreted as a sparer of base (sodium and potassium) when normal acidification fails.

COMMENTS

Derangement of any of the diverse functions of the renal tubule may be considered a focal point of disease in a spectrum of tubular functions [*34*]. The identification of a single defect raises the suspicion of associated defects in functions which may utilize a mechanism or an anatomical site in common with the function found to be abnormal. Thus renal tubular acidosis may be found in association with excessive loss of phosphorus, amino acids and glucose (Fanconi's syndrome), or potassium and calcium wastage, or, very frequently, hyposthenuria. Of the reported cases only one patient was able to concentrate to a specific gravity above 1.020 (Case V of Albright [*3*]), and her urine pH was as low as 5.5, suggesting that her acidifying ability was not severely impaired.

The patient presented herein has failure of urinary acidification without impairment of water reabsorption or the other functions tested. The possible mechanisms underlying this abnormality have been discussed by Smith and Schreiner [*4*] who concluded that a combined defect of hydrogen ion secretion and bicarbonate reabsorption is the most plausible explanation. Since the administration of diamox, an inhibitor of carbonic anhydrase activity, may produce this combination of defects, together with the metabolic changes observed in our patient, the theory that the basic derangement in renal tubular acidosis is a partial failure of carbonic anhydrase activity appears reasonable. The decrease in citrate excretion and the formation of renal stones after prolonged administration of diamox add further support to this theory [*31–33*]. Its proof must await direct assay of carbonic anhydrase in the renal tissue of such a patient.

The excretion of ammonium, although low for the degree of acidosis, was high in relation to

the urine pH. Normally, ammonia (NH_3) is produced in the tubular cells and is excreted in the urine as ammonium (NH_4^+). In acidosis both the production of NH_3, from activation of glutaminase and other enzymes, and the excretion of NH_4^+ are increased [*35*]. The extra H^+ combining with NH_3 to form NH_4^+ also is produced in the tubular cells, by action of carbonic anhydrase on carbonic acid. The site at which H^+ combines with NH_3 and the manner in which NH_3 or NH_4^+ reaches the tubular fluid are unknown. Two theories have been formulated: (1) Free NH_3 diffuses passively from the cell to the tubular fluid, where it forms NH_4^+ by combining with H^+, which previously was derived from the cell by ionic exchange with Na^+ from the glomerular filtrate; (2) NH_3 combines with H^+ while still inside the cell, and the NH_4^+ formed reaches the tubular fluid by ionic exchange with filtered Na^+.

The first theory postulates a gradient for NH_3 between cells and tubular fluid which is maintained by the conversion of diffused NH_3 into NH_4^+, which has the effect of removing the NH_3 from the tubular fluid, allowing more to diffuse from the cells. In acidosis the increased availability of H^+ in the tubular fluid increases the rate of conversion and, hence, of diffusion of NH_3. The inverse correlation between NH_4^+ excretion and urine pH is well supported by experimental work [*13,36*]. If the urine pH is not low, the scanty H^+ ions available are quickly used up, and the NH_3 concentration in tubular fluid increases, reducing the gradient between cells and lumen and, consequently, the rate of diffusion. However, an increase in the rate of urine flow expels the ammoniated tubular fluid so rapidly that the concentration of NH_3 in the lumen does not approach that in cells, and the gradient and rate of diffusion are increased. Orloff [*36*] has shown that, in dogs, NH_4^+ excretion is increased by increasing urine flow when the urine pH is above 6.25.

In our patient NH_4^+ excretion generally changed inversely with the urinary pH (Fig. 3), but NH_4^+ excretion continued at high pH, when it should have ceased. It is likely that the basal rate of ammonia production was increased. The constant state of mild acidosis was probably an effective stimulus of glutaminase activity, and the production of ammonia within the tubular cell must have been high throughout. Pitts [*13*] found that chronic acidosis resulted in the excretion of more ammonia than did acute acidosis. This is probably the result of an adaptive increase in glutaminase activity which has been demonstrated to require several days to reach a maximum [*35*]. Experimental induction of chronic acidosis in rats by prolonged administration of diamox leads to a large excretion of

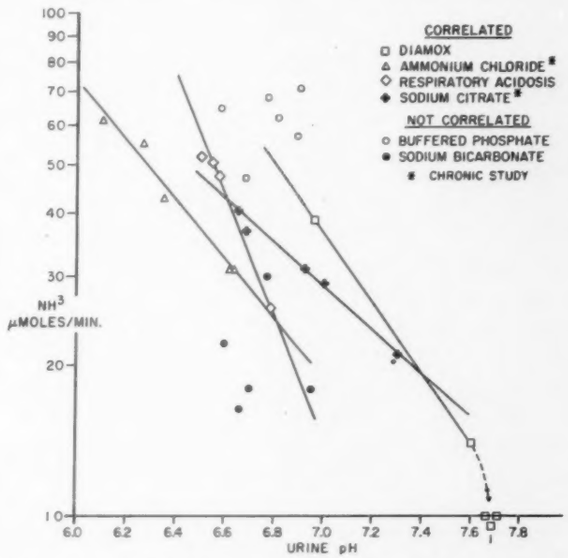

FIG. 3. Relationship between urinary ammonia and urinary pH in various experiments.

ammonia into a urine of relatively alkaline pH, and the suggestion has been made that in this situation the rate of ammonia excretion depends mainly on the rate of ammonia production [*37*]. It seems reasonable to us to consider our patient to be similar, in that ammonia production rather than ammonia diffusion defines the rate of ammonium excretion.

If one accepts the theory of passive diffusion of ammonia, one must assume that in our patient the production within the cell was so great that a diffusion gradient was maintained; i.e., the concentration of NH_3 in the lumen, although high, could receive more NH_3 from the still higher concentration in the cell. If this were the circumstance, reduction in the concentration in the lumen by a more rapid urine flow should cause further widening of the difference in concentrations and an increased rate of diffusion and excretion. However, this was not the case. On two occasions when the urine pH was 6.60 to 7.00, varying the urine flow from 0.5 to 15.1 ml./minute by water loading caused essentially no change in NH_4^+ excretion.

The second theory does not require that NH_4^+ excretion cease, no matter what the pH of the

urine, so long as NH_3 production continues. In this case NH_4^+ excretion does not depend on urine flow. The limiting factors for the excretion of any given amount of NH_3 produced appear to be (1) the availability of intracellular H^+ to combine with NH_3 and form NH_4^+, and (2) the availability of Na^+ within the tubular fluid for ionic exchange with NH_4^+. In a consideration of the two theories the availability of Na^+ can be ignored because it is a requirement for both. The availability of H^+ depends upon the activity of carbonic anhydrase, which presumably is depressed in our patient since it is depressed during administration of diamox, the condition he mimics. If it is assumed that this patient's carbonic anhydrase activity, although always deficient, is stimulated by systemic acidosis, the continued excretion of NH_4^+ in the resting state, when he already has acidosis, and the increasing excretion of NH_4^+ during induced aggravation of acidosis are compatible with the second theory. With respect to the transport of NH_4^+, the changes within the cell become primary and the pH of the urine incidental.

The formation of an appreciable amount of titratable acid during the infusion of a solution of buffered phosphate remains unexplained. This buffer provides the kidney with a load of phosphate radicals for the formation of titratable acid, but the basic mechanism of conversion of disodium phosphate to monosodium phosphate, which essentially accounts for the rise in titratable acidity, depends on the availability of hydrogen ions. This study confirms the observation made by Pitts [*13*] that carbonic anhydrase inhibitors reduce the excretion of titratable acid during phosphate infusion. Yet if one accepts the theory that renal tubular acidosis reflects a failure of carbonic anhydrase activity, it seems paradoxical that the excretion of titratable acid should be so accelerated during a buffer load. There may be sources of hydrogen ions independent of carbonic anhydrase activity, but this remains highly speculative.

The etiology of this patient's condition may be either congenital or acquired. There are two facts in favor of congenital disease: the persistent urine pH above 6.00 from the time he passed his first stone at the age of twenty-seven and the historical absence of any previous renal disease, specifically pyelonephritis. Unfortunately, there is no record of urine pH during childhood. The absence of a familial incidence militates against a congenital error of metabolism, but does not exclude it. The chronic administration of a carbonic anhydrase inhibitor or chronic pyelonephritis could perhaps produce a renal defect like that exhibited by our patient. The former can be dismissed on historical grounds. The latter possibly cannot be absolutely excluded, but the arguments raised for a congenital disease can simultaneously be advanced against pyelonephritis. Furthermore, it seems unlikely that a recurrent infection would selectively affect the mechanism of urinary acidification without influencing any other function of the distal tubule. The relative frequency of pyelonephritis and the paucity of cases with tubular acidosis is a statistical argument against the etiologic association of the two conditions. Finally, if the pyelonephritis were of such long duration as to antedate the first renal calculus, it probably would have led to progressive renal damage; it is more likely that any renal infection present followed the development of the stone, the result of an inherent tubular defect. All these arguments favor a congenital etiology of our patient's condition.

SUMMARY

1. A case of recurrent nephrolithiasis with hyperchloremic acidosis is presented. The tubular defect was limited to impairment of hydrogen ion excretion and did not involve the mechanisms of urine concentration.

2. The patient presented the paradox of a relatively high rate of ammonia excretion in a urine of elevated pH. It would appear that the rate of production of ammonia and its transport by cation exchange, rather than passive diffusion of ammonia, defined the rate of ammonium excretion in this patient.

3. Partial failure of renal carbonic anhydrase activity might account for the observed clinical manifestations.

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Review

Diagnostic Significance of the Muscle Biopsy*

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SKELETAL muscle may be the site of lesions in many disorders. Involvement of the muscle may be suggested by the presence of such symptoms and signs as pain, weakness, tenderness, atrophy or wasting, and hypertrophy but may occur in the absence of obvious clinical manifestations and can then be established only by the examination of muscle tissue obtained at biopsy or autopsy. The pathologic abnormalities seen may be diagnostic of the disorder or may be non-specific.

Great emphasis has been placed on the diagnostic value of the microscopic study of muscle tissue. During the last several years there have been references to its value in polyarteritis [*1*], rheumatoid arthritis [*2–4*], dermatomyositis and polymyositis [*5–7*], disseminated lupus erythematosus [*4,7,8*], scleroderma [*9,10*], sarcoidosis [*11,12*] and myasthenia gravis [*13*]; and an excellent general survey of muscle pathology has appeared [*14*]. Nevertheless, there remains some doubt as to the diagnostic specificity of many of the changes seen in muscle. For example, arteritis of various sorts is seen in many diseases other than polyarteritis, and inflammation and muscle degeneration in diseases other than dermatomyositis. For this reason a retrospective evaluation of muscle biopsies at the Columbia-Presbyterian Medical Center was undertaken in the hope that the diagnostic use of the muscle biopsy could be placed in proper perspective.

MATERIALS AND METHODS

In the eleven year period from 1946 through 1956, 552 muscle biopsies were carried out for diagnostic purposes in 519 patients with a variety of disorders at the Columbia-Presbyterian Medical Center. One hundred and two of these were performed in eighty-nine patients with neurologic diseases, and will not be considered further except as they relate to the total problem.

The separation of patients into the various diagnostic categories was both prospective and retrospective. Classic and generally accepted clinical diagnostic criteria were used primarily to classify patients. In addition, certain other criteria for diagnosis were utilized, as follows:

(1) Trichinosis—either pathologic proof of the diagnosis (three patients) or a compatible clinical picture supported by a positive trichinella precipitin test or skin test (twelve patients) [*15*].

(2) Sarcoidosis—either pathologic verification of the diagnosis from any tissue (thirty-two patients), or an appropriate clinical picture associated with a positive Kveim test (in ten patients) [*16*].

(3) Polyarteritis—either pathologic proof of the diagnosis from any tissue (nineteen patients), or a "classic" clinical picture without pathologic confirmation (eight patients).

(4) Disseminated lupus erythematosus—either autopsy verification of the diagnosis (five patients), a compatible clinical picture associated with a positive L.E. cell test (eight patients), or (in fourteen patients) a typical clinical picture without autopsy proof or positive L.E. cell test (mostly from the period before the L.E. cell test was available.)

The diagnosis of dermatomyositis did not depend alone on pathologic evidence of muscle involvement. Criteria for this diagnosis required the presence of a systemic disease with muscle and variable skin manifestations. Muscle signs and symptoms included weakness, pain, tenderness, swelling and atrophy and contractures in more advanced cases. Skin manifestations included edema of the eyelids, face or extremities, diffuse or mottled erythema, and patchy eruptions and atrophy of the skin [*6,9*]. These same muscle phenomena in the absence of skin involvement, and not due to other specific diseases, were considered to represent polymyositis [*6*]. Using these criteria of classification, twenty of our patients had dermatomyositis and fourteen had polymyositis. In five patients the diagnosis was confirmed at autopsy; three of these patients had associated neoplasms. Poly-

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myositis and dermatomyositis have been considered jointly in this study.

More than three-fifths of the muscle specimens were taken from the gastrocnemius, primarily because of greater accessibility, although a large number of other muscles were also biopsied. (Table I.) In many patients the biopsy specimens were taken from areas of

TABLE I
SITES OF MUSCLE BIOPSY

Gastrocnemius		338
Deltoid		91
Not specified		32
At surgery		24
Abdominal laparotomy	14	
Sympathectomy	7	
Neck exploration	3	
Quadriceps femoris		23
Pectoralis major		8
Biceps humeri, trapezius, peroneus longus, triceps, gluteus maximus		4 each
Sternocleidomastoid		3
Rectus femoris, soleus, vastus lateralis, latissimus dorsi		2 each
Sartorius, supraspinatus, rectus abdominis, tibialis anticus, obliqus abdominis internus		1 each

objective clinical abnormality, but in others they were taken blind and at random. The specimens were examined by the Surgical Pathology Laboratory of Columbia University College of Physicians and Surgeons as part of its routine activity. At least three levels were cut routinely in all biopsy material, and the sections were stained with hematoxylin and eosin. Special stains were used when necessary.

Multiple biopsies performed on the same patient were considered as one biopsy for the purposes of this study. In most of the multiple biopsies, the several specimens showed the same abnormalities (or lack thereof) on microscopic examination; in the few in which this was not so, the most abnormal section served as the basis for diagnosis. We were concerned with the pathologic findings in the muscle of a given patient, not in a given biopsy.

RESULTS

Tissue removed at muscle biopsy normally includes muscle fibers, supporting connective tissue stroma, and the blood vessels contained in that stroma. There are only a limited number of ways that each of these can respond to injury. Muscle fibers can show degenerative changes, for example, in response to a large number of different stimuli, including even excessive handling during the biopsy procedure. For this reason we have chosen to classify our findings in two ways. First will be considered the general pathologic changes seen in muscle during this study, and following this the pathologic condition of the muscle in specific medical disorders. The general changes can further be subdivided into vascular, interstitial connective tissue, and muscle fiber abnormalities.

TABLE II
VASCULAR CHANGES IN MUSCLE

Arteritis with necrosis in:
Polyarteritis
Disseminated lupus erythematosis
Arteritis without necrosis in:
Polyarteritis
Disseminated lupus erythematosus
Dermatomyositis
Septicemia
Muscular dystrophy
Unknown multisystem disease
Perivascular inflammatory cell infiltration in:
Dermatomyositis and polymyositis
Scleroderma
Polyarteritis
Disseminated lupus erythematosus
Rheumatoid arthritis
Acute rheumatic fever
Drug sensitivity
Sarcoidosis
Raynaud's syndrome
Trichinosis
Acute glomerular nephritis
Hypertensive vascular disease
Thromboangiitis obliterans
Arteriolosclerosis
Myasthenia gravis
Muscular dystrophy
Fever of unknown origin
Other medical disorders of unknown etiology
Arteriolosclerosis in:
Hypertensive vascular disease
Generalized vascular disease without hypertension

General Muscle Pathology. Vascular: Table II lists the vascular abnormalities seen in our study. The most marked involvement of the vessels was that of acute arteritis, with necrosis of the media or entire wall of a small or medium-sized artery, and inflammatory cell infiltration of the wall, with or without granulomas. (Fig. 1.) The "granuloma" consisted of necrosis of exudative cells, fibrinoid collagen change, and proliferation of epithelioid cells and giant cells [*17*]. The inflammatory cells were most commonly lymphocytic, but neutrophilic and eosinophilic polymorphonuclear cells were also seen. Arteritis with necrosis was found in the muscles of ten patients with polyarteritis and one with disseminated lupus erythematosus. Eight of the ten

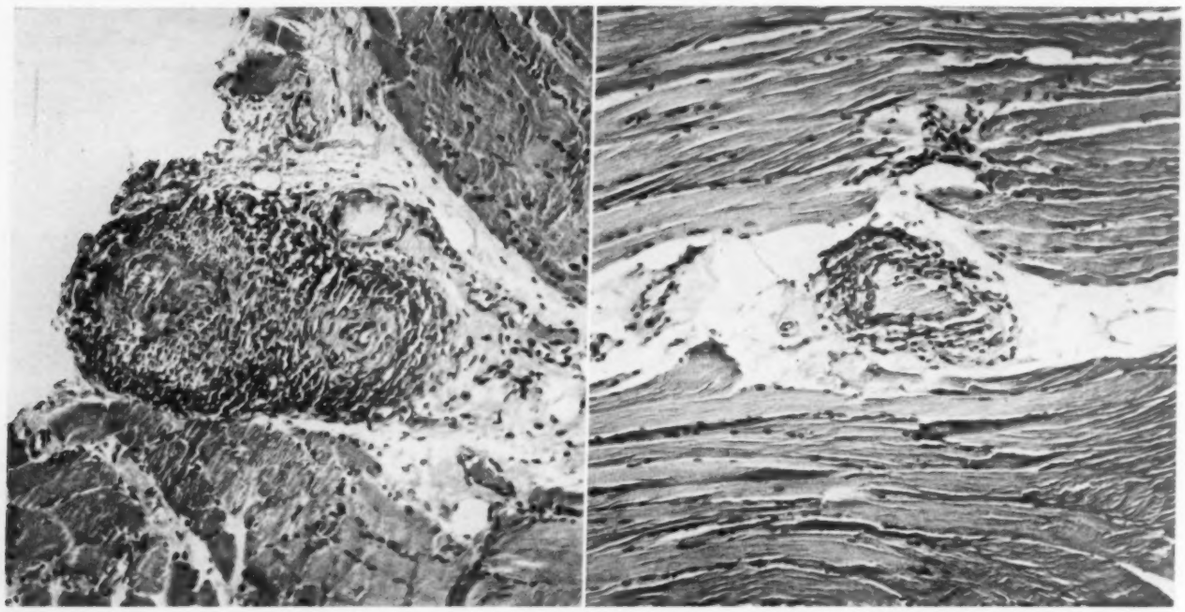

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FIG. 1. Acute arteritis with necrosis in polyarteritis. Hematoxylin and eosin.

FIG. 2. Acute arteritis without necrosis in disseminated lupus erythematosus. Hematoxylin and eosin.

TABLE III
INTERSTITIAL CONNECTIVE TISSUE CHANGES IN MUSCLE

Focal myositis in:
Rheumatoid arthritis
Juvenile rheumatoid disease
Disseminated lupus erythematosus
Scleroderma
Dermatomyositis and polymyositis
Diffuse interstitial inflammation in:
Dermatomyositis and polymyositis
Scleroderma
Polyarteritis
Disseminated lupus erythematosus
Rheumatoid arthritis
Drug sensitivity
Boeck's sarcoid
Subacute bacterial endocarditis
Miliary tuberculosis
Erythema nodosum
Trichinosis
Chronic glomerular nephritis
Chronic pulmonary fibrosis
Myasthenia gravis
Muscular dystrophy
Amyotrophic lateral sclerosis
Diabetic neuritis
Fever of unknown origin
Undiagnosed medical disease
Undiagnosed neurologic disease
Epithelioid cell granulomas with giant cells in:
Boeck's sarcoid
Scleroderma

patients with polyarteritis showed granulomas in muscle associated with the arteritis; granulomas were not present in the remaining two or in the one patient with disseminated lupus erythematosus and arteritis.

Arteritis without necrosis, as defined by inflammatory cell infiltration of the artery wall in the absence of necrosis (Fig. 2), occurred in a larger and miscellaneous group of disorders. Periarterial and periarteriolar inflammatory cell infiltration (more than a simple one cell layer cuffing of the vessel wall) was common. The inflammatory cells were almost always round cells.

Arteriolosclerosis in muscle was noted in four patients, three with severe essential hypertension and one with diffuse vascular disease of unknown etiology without hypertension. One patient with Boeck's sarcoidosis had infiltration of a small artery in muscle by epithelioid cells, lymphocytes and polymorphonuclear cells, without necrosis.

Perivenous and perivenular round cell infiltration was seen, associated with similar changes in the arteries and arterioles. Otherwise no venous abnormalities of significance were noted.

Interstitial connective tissue: The changes in the interstitial connective tissue seen in this study were for the most part inflammatory. (Table III.) Diffuse interstitial infiltration, predominantly

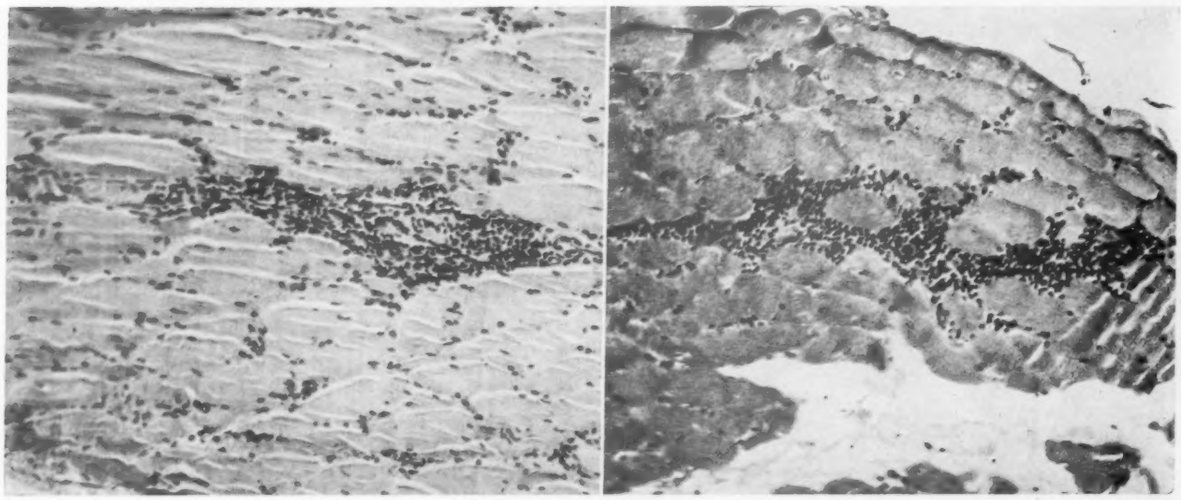

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FIG. 3. Inflammatory and mild degenerative changes in muscle in scleroderma. Note that the central inflammatory lesion fulfills the criteria for focal myositis as well. Hematoxylin and eosin.

FIG. 4. Focal myositis in juvenile rheumatoid arthritis. Hematoxylin and eosin.

lymphocytic in nature (Fig. 3), was the most common lesion found, occurring in a multiplicity of unrelated diseases. In some specimens it was difficult to separate diffuse interstitial, focal or nodular, and perivascular cell infiltration, and in such cases the classification was arbitrary. The separation between these three inflammatory phenomena is undoubtedly artificial. They occurred simultaneously in the muscle in many disorders. The predominant localization of the inflammatory cells was the chief criterion for classification.

The standards of Sokoloff et al. [*18*] as to focal or nodular myositis were used. By these criteria, a circumscribed, compact lesion consisting primarily of lymphocytes, at least 50 in number, measuring at least 35 microns in diameter, and without necrosis, constitutes the nodule of nodular myositis. (Fig. 4.) This lesion was seen in our study in juvenile and adult rheumatoid arthritis, disseminated lupus erythematosus, scleroderma, and dermatomyositis and polymyositis.

The typical lesion of sarcoidosis in the muscle (Fig. 5) is in no way different from that found in other organs and tissues. It consists of one or more usually circumscribed nodules composed of epithelioid cells. Giant cells of the Langhans' type are usually but not invariably present. Slight lymphocytic infiltration is seen in most nodules. Caseous necrosis is not present and tubercle bacilli are never found. Sarcoid-like granulomas were seen in the interstitial connective tissue of muscle in twenty-two patients with sarcoidosis and in one patient with scleroderma.

TABLE IV
CHANGES IN MUSCLE FIBER

Muscle degeneration in:
Dermatomyositis and polymyositis
Scleroderma
Polyarteritis
Disseminated lupus erythematosus
Rheumatoid arthritis
Juvenile rheumatoid disease
Drug sensitivity
Boeck's sarcoid
Subacute bacterial endocarditis
Myasthenia gravis
Miliary tuberculosis
Trichinosis
Chronic glomerular nephritis
Chronic pulmonary fibrosis
Myxedema
Muscular dystrophy
Fever of unknown origin
Undiagnosed medical disease
Undiagnosed neurologic disease
Trichinae in muscle in:
Trichinosis

Muscle fibers (*Table* IV): Degeneration of muscle fibers naturally varies in severity. Early changes include alteration in staining, loss of cross striations, and swelling of fibers. An apparent increase in the number of nuclei and the

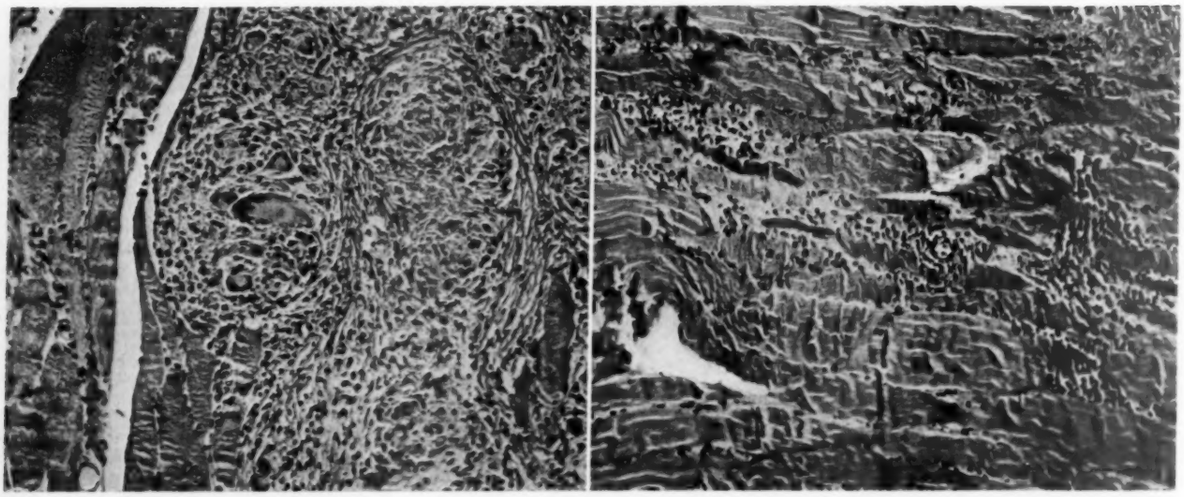

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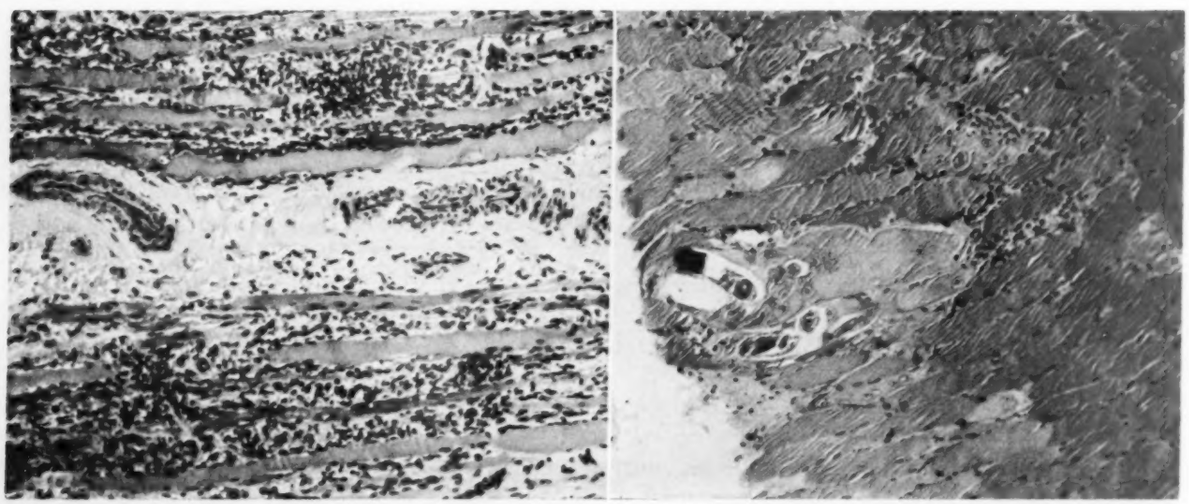
FIG. 5. Diffuse sarcoidal granulomas in muscle. Hematoxylin and eosin.

FIG. 6. Moderately severe muscle degeneration and inflammatory changes in rheumatoid arthritis. Hematoxylin and eosin.



7 8

FIG. 7. Severe muscle degeneration, inflammatory cell infiltration and fibrous replacement in dermatomyositis. Hematoxylin and eosin.

FIG. 8. Trichina larva within muscle fiber. Hematoxylin and eosin.

migration of these nuclei to the center of the fiber is often seen. (Fig. 3.) Later, fragmentation of fibers, granular, fibrinous or vacuolar degeneration (Fig. 6), basophilic metachromasia, and phagocytosis by large histiocytic cells may occur [*6,9*]. Still later, fibrous replacement of the degenerated muscle fibers may be observed. (Fig. 7.)

Minimal degenerative phenomena, occurring only on the fringe of inflammatory cell infiltrates, were very common, but were not sufficiently pronounced to lead to listing in Table IV; more marked and more widespread degenerative changes were necessary for inclusion here. As can be seen from a comparison of Tables II, III and IV, the disorders in which muscle fiber degeneration was noted are essentially the same as those in which diffuse and perivascular inflammatory cell infiltration was found. In a large majority of patients showing any of these phenomena in muscle, all occurred together.

The classic muscle pathologic finding in trich-

inosis is the presence of a trichina larva curled in its spiral form within a fiber. (Fig. 8.) Changes in adjacent muscle fibers include granular, hyaline and hydropic degeneration, followed by an intense inflammatory reaction in surrounding connective tissue, hyperemia and edema [*15*]. In severe infestations the cellular infiltrates may be diffuse but in milder ones they are localized about blood vessels and single muscle fibers. Muscle invasion in acute trichinosis does not usually begin until the seventh day of infection [*15*]. In our study trichina larvae were seen in muscle fibers only in three patients with acute trichinosis. No calcified lesions resembling old trichinosis scars were seen.

TABLE V
TRICHINOSIS (15 PATIENTS)

Trichinae in muscle fibers	3
Inflammatory cell infiltration and muscle degeneration	10
Predominantly round cell infiltration	4
Predominantly eosinophilic and/or neutrophilic polymorphonuclear cell infiltration	6
No pathologic findings	2

Muscle Pathology in Specific Disorders. Tables V through IX give our results with muscle biopsy in specific disorders. As already mentioned, in only three of our fifteen patients with trichinosis (Table V) were trichina larvae seen in muscle. In ten of the remaining twelve patients there were various degrees of muscle degeneration associated with diffuse or perivascular inflammatory cell infiltration; in only six was the cell type eosinophilic or neutrophilic polymorphonuclear.

The muscle findings in Boeck's sarcoidosis are described in detail elsewhere [*19*]. In twenty-two of forty-two patients with this diagnosis (Table VI), biopsy specimens taken at random from apparently uninvolved muscle revealed granulomas. In one patient granulomatous arteritis without necrosis was seen. In three of the remainder perivascular or diffuse interstitial round cell infiltration was noted.

In twenty-five other patients in whom sarcoidosis could not completely be ruled out, although the diagnosis was unlikely in most, none had muscle granulomas. Five patients (two with chronic pulmonary fibrosis, and one each with hilar adenopathy, parotid enlargement and erythema nodosum) showed diffuse perivascular round cell infiltration. Twenty more patients in whom biopsy was performed in an attempt to determine whether or not sarcoidosis was present, but who were shown to have other unrelated diseases, had no abnormalities in the muscle specimen. More complete data on these two groups of patients are also reported elsewhere [*19*].

TABLE VI
BOECK'S SARCOID AND DISORDERS TO BE DIFFERENTIATED FROM IT

Boeck's sarcoid (42 patients):	
Sarcoid granulomas	22
Sarcoid arteritis	1
Perivascular and diffuse round cell infiltration and muscle degeneration	3
No pathologic findings	16
Possible Boeck's sarcoid (25 patients):*	
Perivascular or diffuse interstitial round cell infiltration with or without muscle degeneration	5
No pathologic findings	20
Disorders initially considered as sarcoid† (20 patients):	
No pathologic findings	20

* Including patients with erythema nodosum, uveitis, parotid swelling, hilar adenopathy, chronic pulmonary fibrosis, hepatomegaly and polyarthralgia (see [*19*]).

† Including patients with tuberculosis, ulcerative colitis, congenital syphilis, parotid swelling of various causes, lymphomas, bronchial asthma and pulmonary fibrosis of various causes (see [*19*]).

TABLE VII
POLYARTERITIS (27 PATIENTS)

Acute arteritis with necrosis	10
Acute arteritis without necrosis	4
Healed arteritis	2
Muscle degeneration and perivascular or diffuse interstitial round cell infiltration	3
Muscle atrophy	2
No pathologic findings	6

Ten patients with polyarteritis (Table VII) had characteristic lesions in the muscle, and two others had changes of healed arteritis. Eight of the ten patients with acute arteritis and necrosis of the wall had granulomas present adjacent to the injured vessel. There was no apparent relation between asthma and an increase in eosinophils in these patients and the presence or absence of granulomas. The remaining fifteen patients had non-specific changes in the muscle or none at all. In one hundred sixteen patients muscle biopsy specimens were obtained because polyarteritis was considered in the differential diagnosis. (Table VIII.) None showed lesions of arteritis.

A summary of the muscle findings in other medical disorders appears in Table IX. One patient with lupus erythematosus disseminatus had an arteritis with necrosis (but without granulomas) which was indistinguishable from that seen in polyarteritis. None showed obvious hematoxylin bodies in the muscle. One patient with sclerodoma had multiple granulomas in muscle essentially similar to those seen in sarcoidosis; another patient with scleroderma had muscle calcinosis associated with generalized calcinosis. There were patients in almost all the diagnostic categories listed in Table IX who had muscle degeneration and interstitial inflammatory cell infiltration, although this occurred with greater frequency in the muscles of patients with dermatomyositis and polymyositis. In only four of the patients with the latter disorders, however, were the changes marked and associated with significant fibrosis. Severe muscle degeneration, inflammation and fibrosis identical with that seen in these four instances were also seen in one patient with scleroderma, one with miliary tuberculosis (without tuberculoid granulomas), and one with subacute bacterial endocarditis. In most patients with dermatomyositis and polymyositis and with the other disorders listed, the changes were much less marked.

TABLE VIII
DISORDERS TO BE DIFFERENTIATED FROM POLYARTERITIS (116 PATIENTS)

Renal disease, acute and chronic (23 patients):*	
Muscle degeneration and diffuse interstitial round cell infiltration	1
Perivascular round cell infiltration	1
No pathologic findings	21
Hypertensive vascular disease (22 patients):†	
Arteriolosclerosis	3
Perivascular round cell infiltration	1
No pathologic findings	18
Generalized vascular disease without hypertension (15 patients):‡	
Arteriolosclerosis	1
Perivascular round cell infiltration	1
No pathologic findings	13
Peripheral neuritis (13 patients):§	
Muscle atrophy	3
Perivascular or diffuse interstitial round cell infiltration	2
No pathologic findings	8
Multiple system disorders and fevers of unknown origin (43 patients):	
Perivascular or diffuse round cell infiltration with muscle degeneration	8
No pathologic findings	35

* Including acute and chronic glomerular nephritis, renal acidosis, chronic pyelonephritis, Henoch-Schonlein purpura, nephrotic syndrome, Kimmelstiel-Wilson syndrome, and unknown renal disease.

† All with severe or malignant essential hypertension.

‡ Including thromboangiitis obliterans, generalized arteriosclerosis and multiple embolization.

§ Due to diabetes mellitus, multiple myeloma, lymphosarcoma, and of unknown cause.

COMMENTS

The study of muscle pathology may be of relatively little help in clinical diagnosis in most medical disorders. In this study, only in some patients with trichinosis, sarcoidosis and polyarteritis were pathologic changes seen in muscle which were sufficiently specific for diagnostic purposes. In other patients, the changes seen either were common to many diseases and therefore non-diagnostic, or no abnormalities were noted.

Trichinae were not found in the muscles of patients with disorders other than trichinosis but, on the other hand, only three of fifteen patients with this disease had characteristic muscle lesions on microscopic examination of biopsy specimens. The large majority however, had inflammatory changes in interstitial connective tissue. It has been shown that press preparations of unstained muscle tissue or digestion and centrifugation of the tissue prior to search are preferable to sectioning and staining for discovering trichinae [*20,21*]. In a recent study of acute trichinosis [*21*], in which muscle examination was carried out by these special methods, five of sixteen specimens were estimated to have less than one larva per gram of muscle tissue. Sectioning of the fixed specimen would be unlikely to reveal larvae of such infrequency; adjacent inflammatory changes would be discovered more readily.

Muscle involvement in sarcoidosis has been recognized before [*11,12,22,23*] but the frequency of the finding of sarcoid granulomas in apparently uninvolved muscle has not been appreciated. About 50 per cent of our patients with sarcoidosis had characteristic lesions in muscle. None of our patients had objective clinical changes in the muscles biopsied; four had muscle symptoms, but only two of these had muscle sarcoidosis and two did not. There was a rough correlation between the degree of dissemination of sarcoidosis in other organs and tissues and its appearance in muscle [*19*].

The sarcoid granuloma has been shown not to

TABLE IX

BIOPSY RESULTS IN OTHER MEDICAL DISORDERS

Disease	Patients (no.)	Perivascular or Diffuse Inflammation	Muscle Degeneration	Muscle Atrophy	Arteritis with Necrosis	Arteritis without Necrosis	No Abnormal Findings
Disseminated lupus erythematosus	27	6	3	0	1	1	19
Rheumatoid arthritis	14	2	1	1	0	0	11
Juvenile rheumatoid disease	1	1	1	0	0	0	0
Ankylosing spondylitis	1	0	0	0	0	0	1
Acute rheumatic fever and carditis	10	1	0	1	0	0	8
Scleroderma*	22	7	4	3	0	0	10
Dermatomyositis and polymyositis	34	27	26	1	0	1	5
Drug toxicity and sensitivity	4	2	2	0	0	0	2
Miliary tuberculosis	3	1	1	0	0	0	2
Subacute bacterial endocarditis and septicemia	4	1	1	0	0	1	2
Myasthenia gravis	7	3	1	0	0	0	4
Raynaud's syndrome	5	1	0	0	0	0	4
Miscellaneous medical disorders†	53	3	3	0	0	0	50

* Muscle biopsy in one patient with scleroderma showed sarcoid-like granulomas; in another calcinosis.

† Including "fibrositis," sprue, diarrhea of unknown cause, various liver diseases, malignant melanoma, intestinal obstruction, gout, Behcet's syndrome, myxedema, Cushing's syndrome, multiple myeloma, perinephric abscess, lipoid pneumonia, viral pericarditis, glycogen storage disease, and various skin diseases, eye diseases, and emotional disorders.

be specific for sarcoidosis. Morphologically similar lesions can be produced by systemic tuberculosis, histoplasmosis, coccidioidomycosis, helminth infection, leprosy and, locally, by beryllium, silicon and lipids [*24*]. These disorders, however, do not usually involve muscle. In our study, among those patients without sarcoidosis, sarcoid-like lesions in muscle were seen only in one patient with scleroderma.

The estimated frequency of muscle involvement in polyarteritis ranges from 40 per cent [*25,26*] to 80 per cent [*14*]. These figures represent autopsy incidence of muscle polyarteritis. Maxeiner et al. [*1*] studied 136 muscle biopsy specimens from 106 patients; twenty-six patients were proved to have polyarteritis. In thirteen of the twenty-six muscle biopsy was positive at one time or another, but only 35 per cent of the biopsy specimens from these patients revealed polyarteritis changes. At biopsy, 37 per cent of our patients with proved polyarteritis had muscle arteritis. It is entirely possible that there may be some instances of as yet undiagnosed polyarteritis among the 116 patients listed in Table VIII without pathologic evidence of arteritis. If so, the percentage of positive biopsies will be reduced further.

Churg and Strauss [*17*] described granulomas extravascularly and within vessel walls, in addition to the other polyarteritis vascular changes, in their patients with polyarteritis, asthma and eosinophilia. They did not find similar granulomatous changes in patients with polyarteritis without asthma. Rose and Spencer [*27*] also noted a relationship between pulmonary involvement with polyarteritis and the presence of disseminated granulomatous arteritis. Granulomas were seen in muscle in eight of our patients with polyarteritis, but in this group no correlation with the presence of asthma could be established.

Arteritis with necrosis and inflammatory cell infiltration occurs in a number of disorders other than polyarteritis. It has been described in disseminated lupus erythematosus [*8,28*], rheumatoid arthritis [*29–34*], scleroderma [*35*], acute rheumatic fever [*36,37*] and serum sickness [*38*]. Two other types of arterial involvement have been observed in scleroderma: intimal thickening and proliferation without necrosis or cellular infiltration [*9,10,39,40*] and fibrinoid necrosis of the vessel wall without inflammatory cell infiltration [*40,41*]. Recently, Bywaters [*42*] reported a bland obliterative endarteritis in rheumatoid arthritis resembling that which is seen in scleroderma; similar lesions have also been described in disseminated lupus erythematosus [*8*]. One of our patients with disseminated

lupus erythematosus had an acute arteritis with necrosis, but none of those with rheumatoid arthritis, acute rheumatic fever, scleroderma or serum sickness showed significant arterial lesions in muscle.

No characteristic or diagnostic pathologic lesions were seen in the muscles of patients with the other disorders considered in this study.

Several workers [*8,43,44*] have described, in addition to vascular lesions, certain pathologic changes which may occur in the muscles of patients with disseminated lupus erythematosus. These include fibrinoid degeneration of the connective tissue stroma and the presence of hematoxylin bodies. In only one of twelve muscle specimens in Harvey's series [*8*] and in none of our twenty-seven were similar changes seen.

Freund, Steiner and their co-workers [*45–47*] originally described nodular or focal myositis as a lesion specific for rheumatoid arthritis; and this opinion was shared by others [*48,49*]. Sokoloff et al. [*18*] and several other groups [*3,50–52*] demonstrated, however, that similar lesions occur in the muscles of patients with dermatomyositis, disseminated lupus erythematosus, rheumatic fever, scleroderma, polyarteritis, and also in gout, osteoarthritis, joint tuberculosis, subacute bacterial endocarditis, hypertension, coronary sclerosis, cirrhosis of the liver, and other diseases; in the muscle of patients dying from acute trauma, and in normal persons. Our findings confirm the non-specificity of the lesion.

Diffuse and/or perivascular inflammatory cell infiltration associated with muscle degeneration has been described in dermatomyositis [*6,53–55*], polymyositis [*56–58*], scleroderma [*9,10,40,59–61*], disseminated lupus erythematosus [*4,7,28,62*], rheumatoid arthritis [*4,50*], rheumatic fever [*55*], myasthenia gravis [*13,63–66*], thyrotoxicosis [*61,67*], trichinosis [*15*], pneumonia [*68*], progressive muscular dystrophy [*13*] and myotonia dystrophica [*55*]. In our study similar pathologic findings were seen, in addition to disorders mentioned, in the muscles of patients with polyarteritis and sarcoidosis in the absence of more classic findings, in drug sensitivity, miliary tuberculosis, subacute bacterial endocarditis, chronic pulmonary fibrosis, chronic glomerular nephritis, and in several patients with undiagnosed multiple system disorders. It is clear that the mere presence of inflammatory and muscle degenerative changes is non-specific. Severe inflammatory and degenerative changes with replacement fibrosis were seen more commonly in dermatomyositis and polymyositis than in other disorders, but were also noted in the muscles of patients with scleroderma, miliary tuberculosis and subacute bacterial endocarditis. In any single patient the biopsy findings of muscle degeneration and inflammation cannot be considered specific but must be used along with all other available clinical and laboratory information in making a diagnosis.

SUMMARY

1. A retrospective evaluation of the value of the random skeletal muscle biopsy at the Columbia-Presbyterian Medical Center in the eleven year period from 1946 through 1956 is reported.

2. The changes seen on examination of muscle tissue were of value in diagnosis in some patients with sarcoidosis, polyarteritis and trichinosis.

3. The characteristic lesion in the muscle in sarcoidosis was the epithelioid cell granuloma with giant cells, such as is found in other tissues in this disorder. This lesion was found in muscle in slightly more than 50 per cent of patients with sarcoidosis.

4. In 37 per cent of patients with polyarteritis, acute arteritis with necrosis of the vessel wall, inflammatory cell infiltration, with or without granulomas, was found in the muscle.

5. In only three of fifteen patients with trichinosis were trichinae seen in the muscle specimen obtained at biopsy.

6. In the aforementioned and in other medical disorders, muscle fiber degeneration associated with inflammatory changes was often encountered. Although such lesions occurred with greater frequency and perhaps with greater severity in the muscles of patients with dermatomyositis and polymyositis, they were found in such a wide variety of disorders that they could not be considered to have diagnostic specificity.

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Seminar on the Brain

Contrasting Functions of Limbic and Neocortical Systems of the Brain and Their Relevance to Psychophysiological Aspects of Medicine*

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IT is now such accepted practice to consider psychological factors in the diagnosis and treatment of disease that physicians who have trained since the last war find it difficult to realize that psychosomatic medicine is a development only of the past three decades. The lateness in this development can be attributed to the perpetuation of an old physiological concept that the cerebrospinal and autonomic nervous systems functioned independently of one another. Ironically enough Freud, who was to lead a revolution in psychology which has affected practically every facet of modern life, was so indoctrinated with the teaching that the so-called voluntary and involuntary systems functioned independently that he was unable to perceive the application of his theory to one of the most important aspects of human experience and behavior. Consequently, although he could see a ready explanation of how psychological disturbances could result in hysterical manifestations in parts of the body under the control of the voluntary nervous system, he believed that visceral symptoms could not be psychological in origin [*18*].

This concept won its way into medical doctrine through the teaching of Bichat at the turn of the 19th century [*4*]. Bichat divided the nerves into two great systems, one arising from the autonomic ganglia, which he called the ganglionic nervous system, the other taking its origin in the brain and referred to as the cerebrospinal system. He believed that the ganglia might be looked upon as "so many little brains." He argued that emotions were generated in the internal organs and the little brains controlling them. He pointed out, for example, how anger affected the heart and circulation, grief the respiration, resentment the stomach. Consequently both the organs and the passions were beyond the control of the voluntary nervous system. Owing to the persuasive appeal of Bichat's two independently functioning nervous systems, it was to be more than 100 years before man could dare to hope that he might partially free himself from the ruling passions within himself.

In the forthcoming American "Handbook of Physiology," there will appear a chapter called "Psychosomatics" [*47*]. In adopting the use of this new term, the editors have taken cognizance of a developing specialized field of interest in which neurophysiology has joined hands with psychology, psychiatry and internal medicine. Psychosomatics may be understood to refer to the pursuit of knowledge that is concerned with the explanation of why and how psychological processes find expression through transient or enduring changes in the body. The term thus distinguishes a field of study that focuses attention on mechanisms accounting for changes *within* the body as opposed to those *between* the organism and its external environment. Stated otherwise, psychosomatics is primarily con-

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cerned with the influence of psychological processes on interofective systems.

It will be the purpose of this paper to review some of the recent contributions of neurophysiology to the understanding of psychosomatic problems. Before doing so, it will be necessary first to give a brief analysis of the problem which neurophysiology is peculiarly fitted to explain.

THE PROBLEM FOR NEUROPHYSIOLOGY

Wiener has stated that information is information, not matter or energy [*86*]. It may further be defined as the order that emerges from a background of disorder. In a similar way, it may be said that the *psyche* is information, not matter or energy. In the light of present knowledge, it may be inferred that the central nervous system derives information on the basis of changing patterns of neuronal activity. The patterns are of themselves without substance but they depend on physicochemical processes within nervous tissue.

It is probably the element of subjectivity that most clearly distinguishes psychological functions from other functions of the nervous system. Through introspection we recognize various kinds of information which are appreciated in the form of awareness, feelings, perceptions, emotions and thoughts. At the same time it is evident that numerous informational transactions are carried on within the nervous system without a subjective counterpart.

As information is information, not matter or energy, it is obvious that the informational aspects of the psyche defy physical measurement. Communication from one person to another requires that information find expression through some form of behavior. Behavior is, therefore, the physical correlate of information. Behavior may be broadly defined as any change of an entity with respect to its environment. Starting from there, one can proceed, as Rosenblueth et al. have [*71*], and subdivide various forms of behavior into a hierarchical system. The more orderly a form of behavior, the greater is its potentiality to convey a greater amount of information, i.e., a greater amount of orderliness.

As McCulloch has pointed out, when information is communicated by some form of behavior a loss of information may result [*54*]. He refers to this loss as "corruption" and defines it as the ratio of information in the input of a system to that in its output. This factor of corruption has important implications in the field of psychosomatic research. The corruption in communicating psychic information through the interofective systems is far in excess of that obtaining to the exterofective systems. It is therefore essential when recording the activity of organs, bioelectrical fluctuations of nerve and other tissues, variations in endocrine levels, etc., to demonstrate whenever possible a simultaneous correlation with the external manifestations of the organism's behavior.

Because of his ability to verbalize, man is far preferable to the animal for psychological research. There are, however, great limitations clinically in what can be accomplished in investigating the underlying mechanisms. It is in this latter area that neurophysiology, with its access to animal experimentation, is singularly suited to make a contribution to psychosomatics.

What is the specific problem for neurophysiology? To answer this we must turn again to introspection. *On the basis of introspection it is realized that emotion is the only form of psychological information which, short of physical exercise, is associated with extensive behavioral changes inside the body.* In view of this, it is a matter of first importance to ascertain whether or not one can localize mechanisms in the central nervous system that are particularly concerned with the experience of emotion and its elaboration into behavior. If such mechanisms can be identified, a next step is to inquire how they differ anatomically and functionally from other kinds of neural apparatus. One would then proceed to discover whether or not the underlying central and peripheral mechanisms of emotion can initiate internal changes that are either sufficiently intense or enduring as to result in lesions. Questions related to the formation of lesions, their location and their chronicity are among the most challenging ones with which psychosomatic medicine has to deal.

Information manifest as thought may be derived without an intrusive awareness of bodily feelings. On the contrary, it is the very nature of emotions that they give the sense of pervading the body. Also in contrast to thoughts, only a limited number of emotions can be identified. All the recognized emotions may be considered from the standpoint of *self-preservation* and the *preservation of the species*. Emotions that are informative in regard to threats to self-preservation or to the preservation of the species, and to

the eradication of these threats, are characteristically "unpleasant" in nature. In this category are fear, anger and sorrow. On the other side are pleasurable emotions that are informative of the removal of threats, the active gratification of needs, and the temporary achievement of a state of internal and/or external homeostasis. The emotions of joy and love come conspicuously to mind.

RECENT INVESTIGATIONS ON CENTRAL MECHANISMS OF EMOTION

Comparative neurology indicates that the neural chassis contained within the spinal cord and brain stem caudal to the anterior neuropore is essentially similar in all animals. Physiological studies have shown that this neural chassis contains the basic apparatus required for posture, locomotion, and the integrated performance of mechanisms involved in self-preservation and the preservation of the species. It has long been established that the hypothalamus has neural control over all the interofective systems that account for the visceral and viscerosomatic manifestations which are seen as an accompaniment of emotional behavior. In recent years it has been demonstrated that the hypothalamus also exerts control over the release of pituitary hormones whose influence on the endocrine systems is so vital to self-preservation and procreation. From the experiments of Magoun and others it can be inferred that the neural apparatus within the reticulum of the mid-brain provides the raw stuff of awareness [*51*].

Following the demonstration by Cannon [*9*], Bard [*2*], Hess [*27*], and others of the important role of the hypothalamus in emotional behavior, this little neural structure gradually came to be looked upon as the "center" of emotion. On the basis of findings too involved to go into here, however, there is reason to believe that although the hypothalamus serves as an integrator of emotional expression, it contributes only indirectly to the experience of emotion. The capacity to feel emotion appears to be largely an attribute of the cerebral "driver" embodied in the forebrain which evolves forward of the neural chassis.

Prior to 1936, in line with the views of Cannon [*9*], it was thought that the cerebral cortex was concerned with emotion only insofar as it could inhibit the aspects of emotion under voluntary control. Following the experimental findings of Fulton and Jacobsen that led to the introduction of frontal lobotomy by Moniz [*cf. 20*], this notion was no longer tenable.

From an analysis of the extensive clinical material on frontal lobotomy, it appears that the prefrontal cortex is a neural elaboration that is primarily concerned with anticipation and planning as it applies to both the self and the species. As far as one is able to judge, the relief of emotional symptoms following frontal lobotomy is primarily attributable to the alleviation of anxiety. Anxiety might be defined as the emotional state associated with alertness for and anticipation of future events. It might be inferred, therefore, that emotional guilt feelings are relieved by lobotomy because there is no longer the anxiety that attends anticipation of discovery and punishment for asocial thoughts or acts; that intractable pain, although still experienced, is alleviated because there is no longer the anxiety associated with the anticipation of continued suffering. Similarly, the socially unacceptable behavior which is so frequently seen as one of the undesirable effects of lobotomy might be attributed to an individual's failure to anticipate the consequences of giving expression to his immediate impulses.

The findings in regard to frontal lobotomy led to the assumption that the prefrontal cortex was necessary for the *experience* of emotion. Sole emphasis of this cortex in this respect, however, was hardly justified in view of two considerations: (1) As Lashley has pointed out, the fundamental patterns of emotional behavior appear to have undergone little change in mammalian evolution [*37*]. (2) It would be odd if the prefrontal cortex provided the single cortical substratum of emotion because, in contrast to the phylogenetically old cortex which we are about to consider, it represents one of the formations of the brain that has undergone an extensive degree of development in the evolution of the mammal.

In 1937 Papez published a paper in which he advanced the argument that the phylogenetically old cortex and related structures making up the so-called rhinencephalon provide the anatomical substratum of emotional behavior [*63*]. In 1949 I elaborated on the Papez theory of emotion and postulated a dichotomy in the function of the phylogenetically old and new cortex that might account for differences between emotional and intellectual behavior [*41*]. Reasons were advanced for inferring that the phylogenetically old cortex receives information from

all the intero- and exteroceptive systems and elaborates it into emotional feelings.

The rest of this paper will be devoted to a review of studies on the phylogenetically old cortex and its related structures, which not only demonstrate their importance in emotional and viscerosomatic behavior but also give support to the postulated dichotomy between the phylogenetically old and new cortex. This dichotomy, or "schizophysiology" as it has been called [*43,44*], has important implications not only in regard to the understanding of emotional and intellectual processes but also with respect to psychotherapy and chemotherapy of psychological disorders. As part of this review, we must take up some important anatomical considerations.

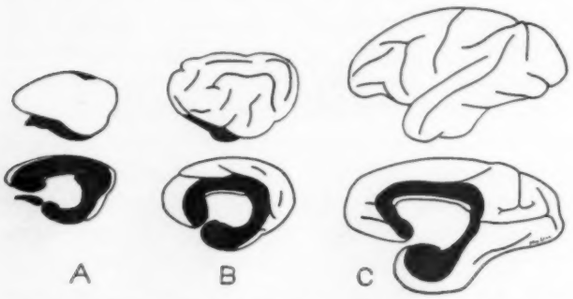


FIG. 1. These drawings illustrate that the limbic lobe, represented in black, forms a common denominator in the brains of all mammals. The medial and lateral surfaces of the rabbit's (A), cat's (B) and monkey's (C) brain are drawn roughly to scale. Note how the limbic lobe surrounds the brain stem. Limbic means "forming a border around." (From MACLEAN, P. D. In: Recent Developments in Psychosomatic Medicine. Edited by WITTKOWER, E. and CLEGHORN, R. London, 1954. Pitman.)

ANATOMICAL CONSIDERATIONS

The structural basis for the aforementioned dichotomy was implicit in the anatomical findings of Broca that were published in 1878 [*8*]. He demonstrated that a large cerebral convolution which he called the great limbic lobe is found as a common denominator in the brains of all mammals. This is illustrated in Figure 1 in which the brains of the rabbit, cat and monkey are drawn roughly to scale and the limbic lobe is represented in black. Broca chose the word limbic as being descriptive of the fact that this lobe "forms a border around" the brain stem. As we shall see, the limbic lobe is also, physiologically speaking, a common denominator of a variety of emotional and viscerosomatic functions in the mammal.

Most of the "old" cortex is contained in the limbic lobe. The faithful reduplication of this cortex throughout the phylogeny of the mammal contrasts with the rapid evolution and growth of the neocortex around it. It has been suggested that the neocortex, in contrast to the limbic cortex, might be likened to an expanding numerator, representing in phylogeny the growth of intellectual functions [*43*].

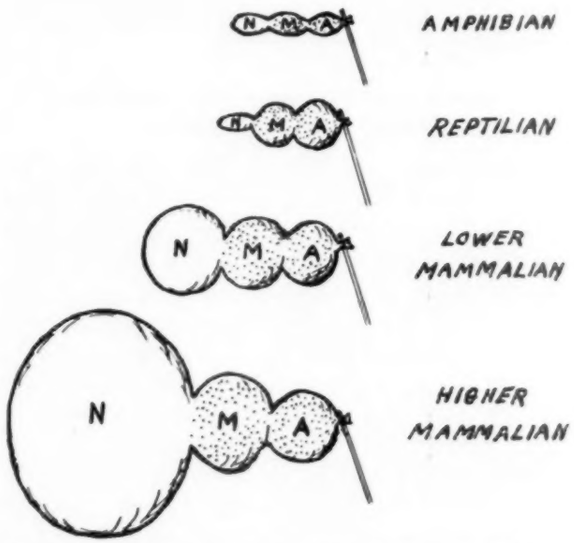


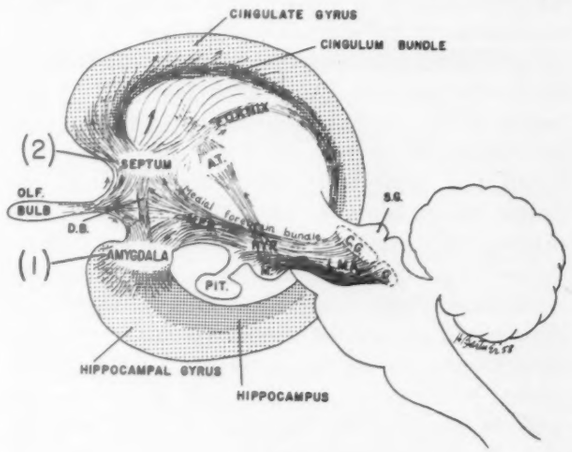
FIG. 2. The uneven expansion of a toy balloon with three segments illustrates the relative growth of the archicortex (A), mesocortex (M), and neocortex (N) during phylogeny. The stick holding the balloon would correspond to the brain stem. The uninflated balloon represents the situation in the amphibian. The archicortex and greater part of the mesocortex (stipple) become folded into the limbic lobe.

One might think of the cerebral cortex as being to the cerebrum what a television screen is to a television set or what a radar screen is to a pilot. Presumably it represents Nature's attempt to give to the organism as clear a picture as possible for making a successful adaptation to the environment. Basically Nature has experimented with three types of cortex, or to use the language of our analogy, three types of screens. They may be appropriately referred to as the archicortex, mesocortex and neocortex. It helps to visualize their evolution if, as in Figure 2, one imagines the blowing up of a toy balloon with three segments. The stick holding the balloon would correspond to the brain stem. The uninflated balloon represents the situation found in

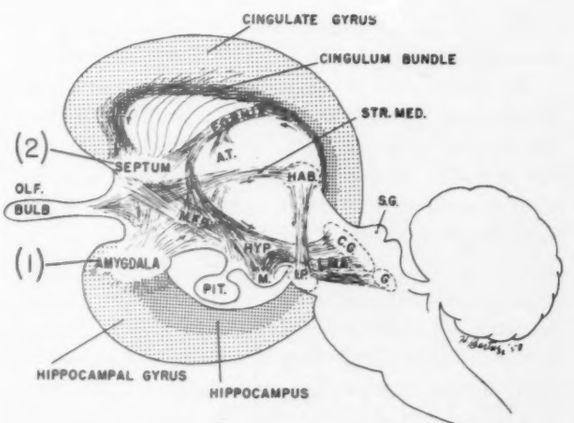
the amphibian. With the appearance of the reptile, there is a ballooning out of the archicortex, so-called because it is the first cortex to differentiate, and there is a considerable expansion of the mesocortex. During the phylogeny of the mammal one of the most striking events of all evolution occurs. This is the great ballooning out of the neocortex. In the process, the archicortex and the greater part of the mesocortex are folded like two concentric rings into the limbic lobe and are relegated, as it were, to the cellar of the brain. The two rings are shown schematically in contrasting stipple in Figure 3. As a result of the large growth of the corpus callosum, the archicortex forming the inner ring (bold stipple) is pulled out somewhat like a piece of chewing gum so that the bulk of it comes to lie in the hippocampus in the inferomedial aspect of the temporal lobe.

At this point three things are to be emphasized. First, the limbic cortex is structurally primitive compared with the neocortex. Radarwise or televisionwise, it therefore might be expected not to present as clear a picture of the environment as the neocortex. Second, it shows essentially the same degree of development and organization throughout the mammalian series. This would suggest that it functions at an animalistic level in both animal and man. Finally, as will be developed in more detail, the limbic cortex, in contrast to the neocortex, has strong reciprocating pathways with the hypothalamus and other ancient structures of the brain stem. This means that there is a strong projection of the visceral as well as the exteroceptive senses onto the old cortical screen. Presumably in an effort to obtain a clearer and better picture for the purpose of adapting to the external environment, Nature fashions the new screen so that it largely portrays what is transpiring in the external world. Finally a point is reached with man where a picture can be represented by word symbols alone. But Nature does not discard the old screens. Presumably having tried them and found them not wanting for the purpose of informing the pilot what his crew and gunners are doing, she holds on to them and keeps them in service.

The medial forebrain bundle and its continuation as the cingulum may be considered to be to the limbic lobe what the internal capsule is to the outer convexity of the brain. In recent years Nauta and his collaborators, using the improved silver technic of Nauta and Gygax, have greatly extended our knowledge of the fine fiber systems making up the medial forebrain bundle, which is schematically illustrated in Figures 3A and B [*58–60*]. It has become evident that the central gray and paramedian reticulum of the mid-brain provide the vital



3A



3B

FIG. 3. Schematic drawings placing emphasis on the medial forebrain bundle (MFB) as a major line of communication between the limbic lobe and the hypothalamus and mid-brain. Note its relation to the fornix and cingulum that become separated through the growth of the corpus callosum. The concentric rings of archicortex and mesocortex are portrayed, respectively, in dark and light stipple. A, ascending pathways to limbic lobe, with emphasis on divergence of fibers from MFB to amygdala and septum. These circuits are labeled 1 and 2 because of special attention given to them in text. B, descending pathways from limbic lobe. A.T., anterior thalamic nuclei; C.G., central gray of mid-brain; D.B., diagonal band of Broca; G., ventral and dorsal tegmental nucleus of Gudden; HAB., habenula; HYP., hypothalamus; I.P., interpeduncular nucleus; L.M.A., limbic mid-brain area of Nauta; M, mammillary body; PIT., pituitary; S.G., superior geniculate.

link between the limbic cortex and the lower brain stem and spinal cord. Indeed, according to Nauta, these structures, together with Gudden's nucleus, deserve the designation of "limbic midbrain area" [*59*]. From these areas there are ascending pathways to various parts of the hypothalamus [*59,60*], and further forward, as illustrated in Figure 3A, there is a divergence of two large streams of fibers from the medial forebrain bundle. One turns laterally to the region of the amygdala where it converges with descending fibers from the lateral olfactory tract. From the amygdala, fibers distribute to the limbic cortex of the frontotemporal region. The other stream runs medially to the septum where it converges with fibers descending from the medial olfactory tract. From here fibers are distributed by way of the fornix and cingulum, respectively, to the hippocampus and cingulate gyrus. As these amygdalar and septal circuits will be singled out for special consideration, they have been respectively labeled 1 and 2 in the diagram. Another important route for traffic to the cingulate gyrus is by way of the mammillary body and anterior thalamic nucleus.

As illustrated in Figure 3B, several of the descending pathways from the limbic cortex to the hypothalamus and limbic mid-brain area run parallel to the ascending ones that have just been described [*58*]. The diagram does not lend itself to portraying diffuse connections from the limbic lobe to the corpus striatum; nor is the stria terminalis shown, an important bundle connecting the amygdala with the septum, preoptic area and hypothalamus. Finally, in view of neuroendocrine observations to be cited, it is to be emphasized that Nauta has recently confirmed Cajal's findings of a sizable bundle of fibers in the fornix that project to the tuberal nuclei which sit astride the portal circulation of the pituitary [*58*].

It has been demonstrated physiologically that the limbic cortex and its immediately associated nuclear structures constitute a functionally integrated system. In keeping with the terminology of Broca, this system has been referred to as *the limbic system* [*42*]. Unlike the term rhinencephalon which has commonly been used to refer to this system, the word limbic, as Broca pointed out, implies no theory in regard to function [*8*]. It also has the advantage of being a short as well as descriptive term.

The rest of this paper will divide itself naturally into two parts. The first part will deal with studies on the localization of function within the limbic system. As will be seen, these studies suggest that respective portions of the limbic system are predominantly concerned with emotionally determined functions pertaining to the preservation of the self or to the preservation of the species. The second part will deal with behavioral, physiological, neuropharmacological and neurochemical studies that concern distinctions between the limbic cortex and neocortex and which lend support to the postulated dichotomy in the function of limbic and neocortical systems.

LOCALIZATION OF FUNCTION IN LIMBIC SYSTEM

No experiment provides stronger evidence of the importance of the limbic system in emotion than the cruel one contrived by Nature. From the study of patients with psychomotor epilepsy, it is evident that epileptogenic foci in or neighboring the limbic cortex may trigger neuronal activity that gives rise to all forms of bodily sensations and imparts to them practically all forms of emotional feelings [*65*].

The Amygdalar Circuit. Patients with epileptogenic foci in or near the frontotemporal cortex fed by the amygdalar circuit (Fig. 3A) experience during the onset of their seizures a wide variety of alimentary symptoms and vivid emotions. The alimentary aura may be a feeling of thirst or hunger or nausea or a peculiar feeling in the epigastrium, whereas the emotional feelings are characteristically of the unpleasant variety associated with the struggle for existence. Feelings of fear, terror, dread and sadness may be combined with a sense of epigastric distress, suffocation, choking or racing heart. I recall the epileptic march of one patient who, following an olfactory aura reminding him of gasoline, experienced a feeling of sadness. This was accompanied by a welling up of tears, which in turn was followed by a feeling of hunger. Sometimes a patient will experience an alternation of opposite feelings, which suggests that there may be a reciprocal innervation of feeling states comparable to the reciprocal innervation of muscles. The automatic behavior that may begin with and follow the various auras is also characteristically alimentary or of the type required for survival. On the one hand, there may be smacking of the lips, drinking, eating, retching, vomiting, or on the other, expressions of terror and flight, rage and fight [*79*].

Experiments in unrestrained and waking animals have shown that one may obtain parallel manifestations upon electrical or chemical stimulation of points throughout the frontotemporal region [*22,32,42,50,57*]. At the time of operation in man or in acute experiments in animals it has been possible to obtain measurements showing the marked autonomic influence of this part of the brain on the pupil [*36*], skin temperature [*12*], respiration [*1,32,40,76*], and the cardiovascular [*1*] and gastrointestinal [*32,82*] systems. Both sympathetic and parasympathetic effects are obtained. Figure 4 illustrates the opposing effects that electrical stimulation of parts of the frontotemporal region may have on pyloric activity. It has been reported that stimulation in the frontotemporal region in man may result in a rise of systolic blood pressure by as much as 80 mm. Hg [*10*].

As one might be led to predict on the basis of stimulation studies, bilateral surgical excisions result in alterations in the way an animal feeds and protects itself [*19,34,68,72,73*]. Monkeys, whose preferred diet is fruit, will eat raw meat or fish after ablation of this region, and wild animals seem to lose their sense of fear and to become tame. They seem to have an incapacity to persist in avoiding things that are painful or harmful to them. A monkey, for example, would, if permitted, repeatedly mouth a burning match. In short, such animals seem to lose the ability to look after their self-protection and to eat properly.

Comment: The foregoing observations, together with the fact that alimentary and self-protective manifestations may be obtained upon stimulation of *intermixed* points in the frontotemporal region, suggest that this portion of the limbic system is primarily concerned with self-preservation as it pertains to survival mechanisms involved in obtaining and assimilating food [*42*]. The representation of these primitive functions in this primitive part of the brain possibly helps to explain the close tie-up between food and emotions that manifests itself in everyday life and which is such a prominent feature in psychosomatic illness. One is reminded, for example, of obese patients who may eat because of feelings of nervousness, fearfulness, or the need of love; or of the hypertensive patient who quarrels and then goes off and eats voraciously a large meal while still in a rage.

Cannon repeatedly emphasized the equivalence of emotion and pain in their capacity to set into play the self-protective mechanisms of the organism [*9*]. The animal's altered behavior in response to pain following frontotemporal ablations raises questions in regard to the functional localization of pain that are of fundamental interest to the internist. It is classically

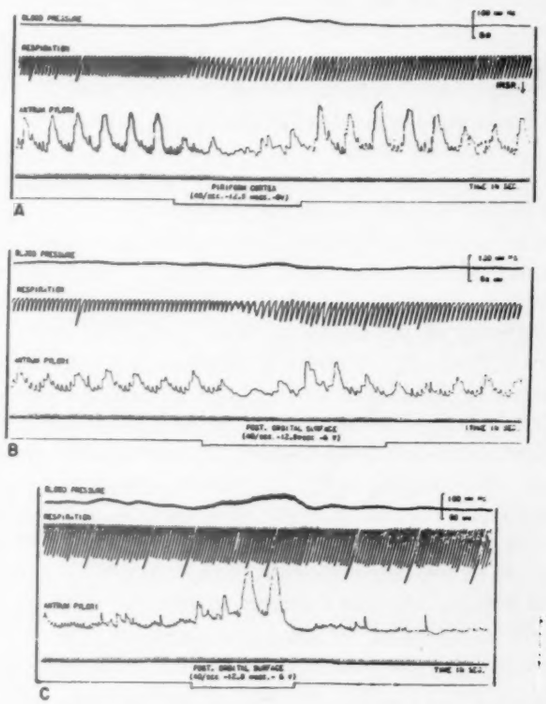


FIG. 4. Recordings from experiments of Kaada, showing effects of electrical stimulation of frontotemporal cortex of limbic system on blood pressure, respiration, and pyloric activity. Attention is directed particularly to opposing effects on pyloric motility. (From KAADA, B. R. *Acta physiol. Scandinav.* (supp. 83) 24: 285, 1951 [*32*].)

taught that the spinothalamic tract and its projections to the ventral posterolateral thalamus and postcentral gyrus represent the anatomical substratum for the psychological appreciation of pain. The recent findings of Mehler, Feferman and Nauta, however, indicate that but a relatively small part of the spinothalamic tract reaches the thalamus [*55*]. Rather, the bulk of the fibers terminate in the reticulum of the medulla and in the central gray matter and other structures of the mid-brain. This would seem to provide an important correlation with recent findings [*56*] which support previous inferences [*77*] that the central gray and closely associated structures of the mid-brain represent a basic part of the primitive mechanism concerned with pain. In the light of limbic cortical and mid-brain interrelationships that were reviewed,

it also gives added significance to the findings that noxious stimulation results in electroencephalographic changes that can be localized to the frontotemporal region [*49*]. There are indications, therefore, that the frontotemporal portion of the limbic system may play an important role in the psychological appreciation of pain. Coupled with the neurochemical and neuropharmacological findings to be dealt with in the next section, these observations have interesting chemotherapeutic implications.

The Septal Circuit. Curiously enough, following ablations of the frontotemporal region, animals may show hypersexuality that is often very bizarre in nature. These findings were first and vividly described by Klüver and Bucy in their classic paper on the effects of ablations of portions of the temporal lobe [*34*]. The reader may find an interesting elaboration on their work by Schreiner and Kling [*73*] and by Green et al. [*25*]. The former observed, for example, that a cat deprived of part of this region would try to copulate with a chicken. Such findings suggest a release of other structures of the brain that are concerned with sexual behavior. This leads to the consideration of the circuit labeled 2 in Figure 3A and referred to here as the septal circuit because it involves *parts* of the hippocampus and cingulate gyrus that receive their nerve supply by way of the septum. In a series of investigations involving chemical or electrical stimulation of this system of structures we have observed enhanced pleasure and grooming reactions and sexual manifestations, including penile erection. How these behavioral manifestations are correlated with the various stages of the electroencephalographic changes seen with chemical stimulation and with the intensity of electrical stimulation is too complicated to go into here and the reader must be referred to the original papers [*43–46*].

Except for von Bechterew's mention of experiments in which his collaborator Pussep elicited penile erection in the dog upon stimulation of the anterior part of the thalamus, we know of no previous report of findings of this kind upon stimulation of the brain [*84*]. Hess and Meyer have recently reported that they elicited grooming upon stimulation of the septum and cingulate gyrus [*28*]. Olds and Milner have made the striking observation that rats with electrodes implanted in the septum and in a number of other limbic structures will repeatedly press a bar to obtain electrical stimulation of the brain [*62*]. These findings have been confirmed and extended by Brady [*6*] and Lilly [*39*] in the cat and monkey. In the discussion following a paper which Olds gave at a recent Ciba Conference I asked him if he had ever seen erections in his animals. He replied: "In about one-third of our animals we get erection; and almost always when we get erection we get self-stimulation. . . . We almost invariably get the enhanced grooming after the stimulus" [*61*]. Lilly has presented a striking motion picture of a monkey repeatedly having an erection upon electrical stimulation within the system of structures under consideration.

Erickson has reported a case of hypersexuality in a fifty-five year old woman who had a tumor in the paracentral lobule which impinges upon the posterior cingulate gyrus [*13*].

Comment: From the foregoing observations, it might be inferred that a portion of the limbic system involving related parts of the septum, hippocampus and cingulate gyrus is concerned with expressive and feeling states that are conducive to sociability and other preliminaries of copulation and reproduction. In other words, this portion of the limbic system, in contrast to the frontotemporal region, appears to bear on activities that are directed for the purpose of preserving the species rather than the self.

From the clinical point of view these recent findings raise the following provocative questions: How are they to be regarded in the light of the relief of tension, sometimes compared to the feeling state after orgasm, that some patients experience following psychomotor seizures? How are they to be considered with respect to the localization of morbid function expressing itself as hypersexuality and euphoria in psychotic behavior? What possible relevance do they have to the beneficial effects of electroshock treatment, in which, as first noted by Jung [*31*], the hippocampus is especially prone to seizure discharge?

Neuroendocrine Aspects. In view of the evidence of functional localization in the limbic system with respect to self-preservation and the preservation of the species, the hypothesis was suggested in 1955 that the frontotemporal region may exert a discriminatory influence over the release of such hormones as ACTH by the hypothalamo-pituitary system during times of stress, whereas the structures fed by the septal circuit may serve in a parallel capacity in regard to sexual hormones [*44*].

Recently Mason has reported that electrical stimulation of the amygdala results in a marked elevation of the plasma 17-hydroxycorticosteroid levels which are almost comparable to those seen after stimulation of the infundibular portion of the hypothalamus. The findings in three monkeys are graphically illustrated in Figure 5. In contrast, he has made the highly significant observation that stimulation of the hippocampal fornix system appears capable of exerting a prolonged suppressive action, lasting as long as forty-eight hours, on the pituitary adrenocortical system and seems to be involved in the maintenance of normal diurnal rhythm in ACTH secretion. Koikegami et al. have reported that bilateral amygdaloidectomy in puppies results in a generalized atrophy of the endocrine glands [*35*].

Turning now to the septal circuit, one finds that in 1939 Harterius reported that electrical stimulation in the region of the septum induced ovulation in the rabbit [*26*]. Recently Stamm has observed that female rats following bilateral ablations of the cingulate gyrus fail to nurse their young [*78*].*

FINDINGS PERTAINING TO THE POSTULATED DICHOTOMY IN FUNCTION OF THE LIMBIC AND NEOCORTICAL SYSTEMS

Feelings and emotions provide us with the connecting bridge between our internal and external world. In other words, it is such experience that assures us of the reality of ourselves and the environment around us. A crazy man would be crazy not to believe in the reality of his crazy feelings. There are clinical and experimental indications that without the structures comprising the limbic system we would be like disembodied spirits.

Limbic Seizures in Man. Patients with psychomotor epilepsy may have seizures in which the neuronal disturbance is largely confined to limbic structures. During the automatisms associated with such seizures, patients may give themselves severe burns because they are apparently insensible to the noxious stimulus. They may eat the things which ordinarily would be obnoxious to them. Some patients may carry out intellectual and highly skilled performance. For example, there is Hughlings Jackson's famous case of a young doctor who, during a psychomotor seizure, examined a patient and wrote a correct diagnosis and prescription, all without having any memory of what had happened [*30*]. I vividly recall an engineer who took his train safely from 125th Street to Grand Central Station during a seizure. As in all such cases, there was an amnesia of what had happened. It would seem that the neural circuits essential for registering visceral and bodily feelings, and the memories compounded out of them, were disrupted during such seizures. Recently there have been clinical reports emphasizing that destructive lesions or ablations of the hippocampus are associated with impairment of recent memory and other manifestations of Korsakoff's syndrome [*66,74,80,85*]. It has been recognized for many years that lesions of the mammillary bodies which are strongly connected with the hippocampus are a common finding in this syndrome.

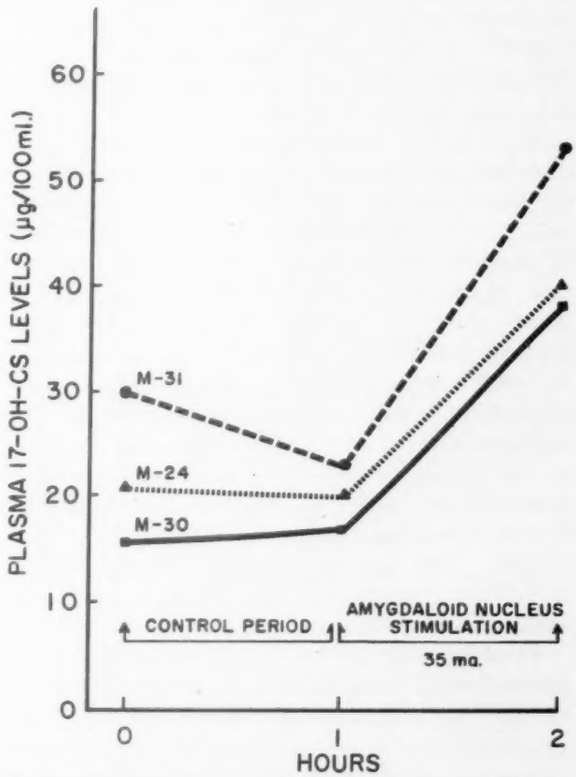


FIG. 5. Illustration from paper by Mason, showing plasma 17-hydroxycorticosteroid response to stimulation of the amygdala in three monkeys. (From MASON, J. W. In: Henry Ford Hospital Symposium, Reticular Formation of the Brain. Boston, 1958. Little, Brown & Co. [*53*].)

Hippocampal Seizures in Animals. The most striking demonstration of the neural integration

* The reader who wishes to pursue this subject further is referred to a recent review article by Gloor [*23*].

of limbic structures and the potential dichotomy in function of the limbic and neocortical systems is provided by mapping the spread of an afterdischarge induced by electrical stimulation of the hippocampus. Such discharges have the tendency to spread throughout and to be largely confined to the limbic system and perilimbic structures [*32*]. One might imagine that the impulses of the discharging neurons are like stampeding bulls which do not stampede beyond the corral of the limbic system. Such seizure activity may be looked upon as producing what must amount *in part* to a "functional ablation" of the limbic system because the neural circuits are occupied by a meaningless discharge and are out of commission for communicating the normal flow of impulses. Theoretically, therefore, the study of intact waking animals during hippocampal seizures provides a means of assessing the effect of deprivation of limbic function on behavior. Despite the intense nature of the seizure recorded electrically, there may be little or no evidence of convulsive activity in the body musculature. There is, however, an apparent loss of an animal's ability to respond to various stimuli, and pseudocatatonic manifestations, somewhat reminiscent of what is seen in schizophrenia, are a striking feature [*43,44,46*].

In order to obtain an objective measure of the psychological impairment, we undertook a variety of conditioning studies. During the propagation of short-lasting electrically induced seizures, animals that have been trained in a shuttle box to avoid a shock following the sound of a buzzer will fail to respond to the buzzer, but will frequently direct their escape upon receiving the shock [*48*]. Relatively simple conditioned reflexes, such as conditioned cardiac and respiratory reflexes and leg withdrawal, are also abolished during propagating hippocampal seizures [*16,48*]. There is evidence that when there is poor propagation of the discharge to the limbic structures of the opposite side there may be a partial or complete retention of the conditioned response. This suggests that there must be a massive alteration of function in limbic structures of both sides if the animal is to fail altogether in responding to the conditioned stimulus.

Brady and Nauta [*7*], Pribram and Weiskrantz [*69*] and others have performed surgical ablations of various parts of the limbic system and have demonstrated marked alteration in the conditioned performance of animals.

Comment: Gantt has observed that of all conditioned reflexes the cardiac reflex is most resistant to extinction [*21*]. In his words, the organism remembers with its heart, but not with specific movements. This has important psychosomatic implications which are best suggested in a continuation of what he says: "Thus," he points out, "the emotional basis for action remains after the external and superficial movements of adaptation have been lost . . . The organism is being pounded by past emotional memories, which prepare it for an act no longer required." On the basis of clinical and experimental findings it may be inferred that the hippocampus has an important part in laying down such memories.

Electroencephalographic Findings. Electrophysiological studies have shown that parts of the hippocampal gyrus [*49*] and hippocampus [*24,38*] under certain conditions manifest distinctive rhythmic potentials that contrast with the low voltage fast random activity appearing simultaneously from the cortex elsewhere. For example, when an animal is aroused or alerted, slow rhythmic activity appears in the electroencephalogram recorded from a large segment of the hippocampus. Similar changes are seen following natural or electrical stimulation of the various intero- or exteroceptive systems.

Neuropharmacological Findings. In view of such electroencephalographic differences, we undertook to learn whether or not the action of various tranquilizing and psychotomimetic drugs could be correlated with a differential action on limbic and neocortical systems as revealed by changes in bioelectrical activity.

Reserpine: The administration of a single large dose of reserpine to cats resulted in electroencephalographic changes that could be localized to the hippocampus and the region of the hypothalamus [*48*]. These changes were characterized by the appearance of slow rhythmic potentials that persisted throughout periods when the neocortex showed low voltage, random fast activity. The frequencies of these potentials slowed from a range of 3.5 to 4 per second to 2.5 to 3.5 per second during the first twenty-four hours. During the subsequent four to five days, when the animal was recovering from the effects of reserpine, one saw a gradual reversal in the course of these electroencephalographic events. It was of interest to find that, except for the extended time course, the electroencephalographic picture associated with reserpine has

many similarities with that observed during the induction and recovery stages of ether anesthesia. Of the agents we tested, ether and reserpine were the only ones that were associated with this distinctive type of electroencephalogram.

Using different doses and different electroencephalographic criteria, Killam, Killam and Thomason [*33*] and others also have been able to demonstrate a differential action of reserpine on the limbic system.

Bulbocapnine and Other Drugs: We found that the administration of bulbocapnine resulted in spiking activity in the cingulate gyrus and the hippocampus. Other agents, including lysergic acid diethylamide (LSD) chlorpromazine and iproniazid did not produce electroencephalographic changes of a localizing nature.

Comment: The foregoing observations are of interest in the light of our findings that the administration of reserpine or bulbocapnine, like propagated hippocampal seizures, results in the loss of conditioned cardiac and respiratory responses [*16*]. The neurochemical observations that will now be described suggest further correlations.

Neurochemical Findings. With the publication in 1956 of the neurochemical findings of Pletscher, Shore and Brodie [*67*] it became apparent that the evolution of the electroencephalographic changes seen with reserpine followed a time course strikingly similar to that of the depletion and restoration of 5-hydroxytryptamine (5-HT) in the brain which these authors found after administering large doses of reserpine to rabbits. In view of this, we made a study of the 5-HT content of the hippocampus and other cortical and subcortical structures of the limbic system [*64*]. Heretofore it had been claimed that the amount of 5-HT in the cerebral cortex was negligible compared with that in the hypothalamus and other parts of the brain stem. We found a relatively high value of 5-HT for the hippocampus, and the values for the medial pyriform cortex and the amygdala were higher than those for the hypothalamus. Figure 6 allows one to see at a glance the comparative values of representative areas of the neocortex and limbic mesocortex. One will note that as one proceeds around the limbic lobe in either direction away from the olfactory trigone there is a fall-off in the values of 5-HT. In a smaller sampling of limbic structures, Bogdanski et al. obtained comparable findings with a different method of assay [*5*].

Comment: In view of current speculations about the role of 5-HT (serotonin) in the psychoses, these findings are of considerable interest. They will remain largely of descriptive interest, however, until something definite is known

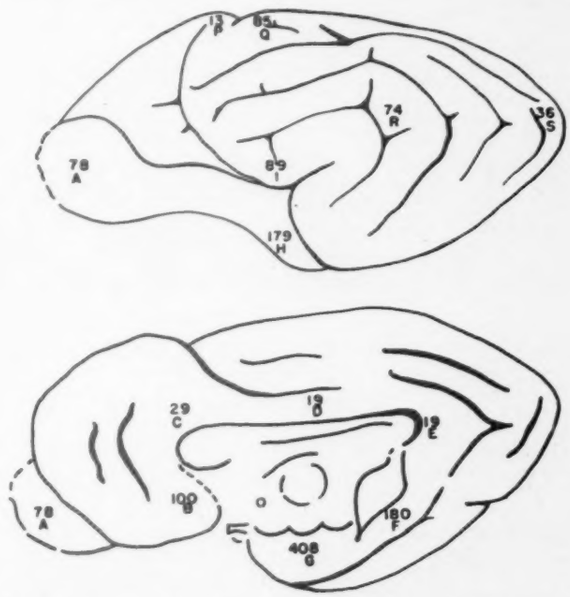
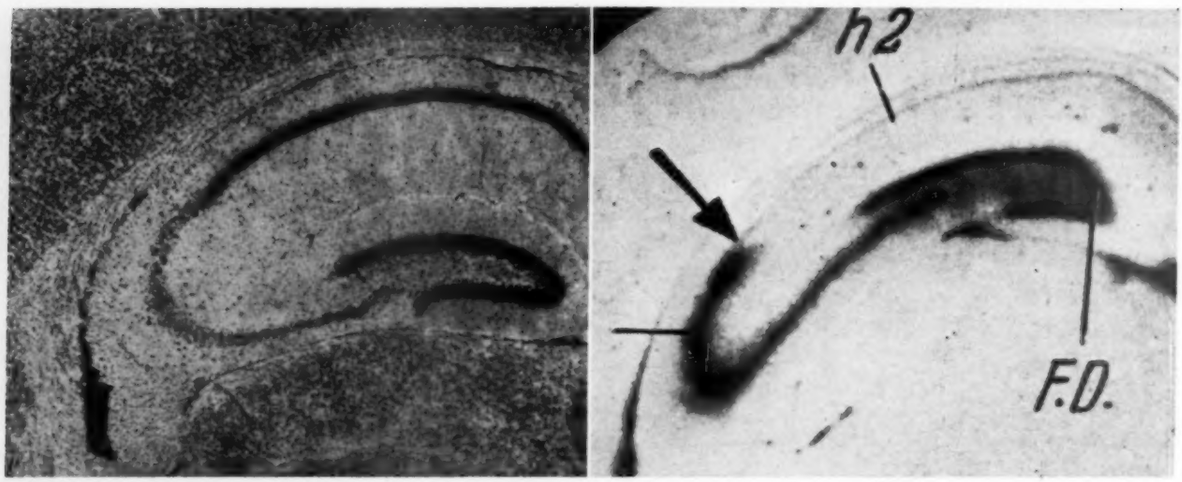


FIG. 6. Lateral (top) and medial (bottom) surfaces of dog's brain showing values of 5-hydroxytryptamine (serotonin) in representative areas of the limbic mesocortex and the neocortex. Values are micromilligrams of serotonin per gram of tissue. A, olfactory bulb; B-I, special areas of limbic cortex; P and Q, sensory-motor cortex; R, auditory cortex; S, visual cortex. Note fall-off in values as one proceeds from G in either direction around limbic lobe. (From PAASONEN, M. K., MACLEAN, P. D. and GIARMAN, N. J. *J. Neurochem.*, 1: 326, 1957 [*64*].)

about the part that 5-HT plays in cerebral function.

Cerebral radioautography: In a cerebral radioautographic study employing S^{35}-labeled l-methionine, we found that the incorporation of S^{35} in the limbic cortex generally, and in the hippocampus in particular, was considerably higher than in the neocortex [*14,48*]. These findings suggest that the limbic cortex has a higher turnover of protein than the neocortex. It was found that insulin convulsions, reserpine, barbiturates and infection depress the uptake of S^{35} in the brain. The changes in some instances were suggestively greater in structures such as the hippocampus that normally show high radioactivity.

Comment: The foregoing observations raise questions of therapeutic interest to the internist. In discussing the results we stated: "The radio-



7A 7B

FIG. 7. These two photographs illustrate the striking finding that 3-acetylpyridine, an antimetabolite of nicotinamide, destroys the neurons in the same area (H3 of the Vogts) of the hippocampus that is stained by dithizone, a chelating agent which gives a reddish color when combined with zinc. A, from an experiment by Coggeshall and MacLean [*11*], showing complete loss of neurons in H3 of mouse treated with 3-AP. B, part of a photograph from paper by Fleischhauer and Horstmann, showing staining of the same area in guinea pig with dithizone. Arrow points to junction between H2 and H3. (FLEISCHHAUER, K. and HORSTMANN, E. *Ztschr. f. Zellforsch.*, 46: 598, 1957 [*15*].)

autographic picture seen in cases of infection is suggestive that a depression in the anabolic phase of metabolism may be a contributing factor in the symptomatology related to the nervous system during infectious, febrile diseases, e.g., lassitude, apathy, delirium. In the light of this possibility it would appear to be a matter of great practical importance to employ radioautographic methods to test the therapeutic hypothesis that the provision of an abundant supply of readily assimilated nutriments is conducive to restoring the anabolic phase of protein metabolism.

"The results of the studies on infection and convulsions, when considered together, raise questions that bear on the predisposition of some children to seizures during febrile illnesses. Do untoward changes in protein metabolism during the illness make the patient more susceptible to seizures? Do the seizures, in turn, aggravate an already deleterious process?" [*14*].

3-Acetylpyridine: 3-acetylpyridine (3-AP) is an analogue of nicotinic acid, and it has been suggested that it may act as a competitive antagonist of the antipellagra vitamin [*87*]. In 1955 Hicks reported that administration of 3-AP resulted in destruction of cells in the hippocampus, the extent of which was not specified [*29*]. This suggested to us the possibility of using the delicate fingers of Nature to make lesions in the hippocampus and thereby afford us the possibility of observing the effects of such destruction on behavior. In a pilot study Coggeshall and I found that the administration of a single intraperitoneal dose of 3-AP to *non-inbred* mice resulted in the destruction of hippocampal neurons in the area designated H3 by the Vogts [*11*]. Fifteen of twenty mice showed lesions in this area. In some, damage was irregularly present in other areas of the hippocampus and in the dentate gyrus, but not elsewhere in the brain. Figure 7A shows the histological picture in one of the cases in which there was a complete loss of neurons in H3.

Curiously enough, dithizone, a chelating agent which gives a reddish color when combined with zinc, stains and sharply demarcates the same area of the hippocampus destroyed by 3-AP.* This is illustrated in Figure 7B showing part of a photograph from a paper by Fleischhauer and Horstmann [*15*] who have recently extended the original observations of Maske [*52*].

It is also of relevant interest that Barlow and co-workers have found that the administration of C^{14}-labeled isoniazid (isonicotinic acid hydrazide) leads to high radioactivity in the hippocampus [*3*]. Isoniazid is a congener of iproniazid, a so-called psychic energizer, which inhibits one of the enzymes that participates in the destruction of serotonin, noradrenalin, and other

* The pancreas also stains red.

amines. As already mentioned, the hippocampus is one of the limbic structures having a high content of serotonin.

Comment: One cannot review these findings without being reminded that chronic nutritional deficiency resulting in pellagra and characterized by the lack of niacin may be complicated by psychotic manifestations. The striking predilection of 3-AP and dithizone for the same area of the hippocampus also leads one to think about the possibility that this part of the brain may contain a dehydrogenase involving zinc. *In vitro* studies by Kaplan and his collaborators suggest that the active site of DPN-dependent systems may involve an interaction of sulfhydryl groups and zinc [*83*].

Recently Vallee has demonstrated marked abnormalities of zinc metabolism in patients suffering from postalcoholic cirrhosis [*81*]. Emphasizing that zinc is a component of alcohol dehydrogenase, he hypothesizes that the alcohol dehydrogenase of the liver is particularly vulnerable to repeated metabolic insults by high concentrations of alcohol. If it were to be found that the presence of zinc in the hippocampus was also owing in part to alcohol dehydrogenase, it would be tempting to think of a similar hypothesis in regard to this structure and the symptoms of Korsakoff's psychosis seen in alcoholism. One will recall in the clinical evidence already referred to that patients with destructive lesions of the hippocampus show impairment of recent memory and other manifestations of Korsakoff's syndrome.

CONCLUDING COMMENT

The emphasis given to the dichotomy in function of the limbic and neocortical systems should not lead to the impression that they work independently of one another. At the subjective level, one suspects that their communication problem is a little like that of a horse and rider. But just where in the brain this metaphorical interplay takes place is not clear. As Nauta has stated in his most recent paper, "In spite of much speculation, the anatomical substratum for . . . neocortico-limbic interaction is almost entirely obscure; it would seem to hold a lively challenge for future investigation" [*59*].

On the basis of clinical and experimental evidence, it has been suggested that the central gray matter and reticulum of the mid-brain provides one of the most likely meeting places [*42*]. Nauta's recent studies [*58,59*] point in this direction, and the physiological investigations of Green and Arduini [*24*], French, Hernández-Peón and Livingston [*17*], and others provide dynamic evidence in support of such an hypothesis. Another likely meeting place is in the diffuse projection system of the thalamus.

Reverting to our original television analogy, one might think of the primitive cortex—the first cortex Nature experimented with—as being comparable to one of the crude, 9-inch screens in the early days of television. In contrast, the evolving neocortex might be likened to the ever expanding screens which the television industry continues to develop. Further, we might think of the old cortex, the old screen, as giving a muddied picture of the internal and external environment in terms of emotional feelings; whereas the evolving neocortex provides an ever clearer picture in the form of discriminative thought. But here the analogy ends, because the cortical screens are presumed to play back on a common cone within the brain stem. Through such reciprocity of action, one could visualize a mechanism whereby emotion might facilitate or paralyze thought, or by which thought might generate or control emotion. Such a relationship would also provide a possible mechanism by which the frontal lobes contribute to the anticipatory aspects of emotion, and in addition obtain the insight which is necessary for the foresight that looks to the need of others, as well as the self.

SUMMARY

An analysis is made of problems pertaining to psychosomatic medicine the explanation of which requires the help of neurophysiology. This analysis turns the focus of attention on the question of central mechanisms of emotion. A summary is given of the work in this area that has led to investigations on the phylogenetically old cortex and related structures which collectively are referred to as *the limbic system*. This designation is explained in the course of presenting a short anatomical introduction to the physiological material.

The rest of the article is divided into two parts. The first part deals with investigations on the localization of function within the limbic system. These studies suggest that respective portions of the limbic system are concerned with emotionally determined functions pertaining to the *preservation of the self* or to the *preservation of the*

species. Neuroendocrine aspects of limbic function are included in this part.

The second part presents behavioral, physiological, neuropharmacological and neurochemical findings pertaining to a postulated dichotomy in the function of the limbic and neocortical systems.

As indicated in the accompanying comments, this material has important implications not only in regard to understanding differences in emotional and intellectual processes but also with respect to the psychotherapy and chemotherapy of psychological disorders.

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Clinico-pathologic Conference

Complications of Diabetes Mellitus

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A WHITE male insurance broker, thirty-seven years of age, was admitted to Barnes Hospital for the third time on December 23, 1957. He died on December 24. His chief complaints at this time were vomiting, diarrhea and nausea of two to three days' duration.

The patient's first admission to the hospital was from December 18 to December 23, 1956.

Diabetes had developed at the age of nine years, and he had been maintained on insulin and dietary regulation thereafter. At puberty (age thirteen to fourteen) he had experienced occasional episodes of acidosis. His maximum insulin requirement had never been in excess of 45 units daily. Two years prior to this admission his vision had begun to fail and he had became totally blind six months prior to admission. The patient had had edema of the ankles one year prior to hospitalization but none immediately prior to admission. He had been taking 10 units of lente insulin each morning and evening and 24 units of regular insulin each morning, for some time prior to admission. He had received a blood transfusion about December 4, 1956 because of anemia. In the one to two weeks prior to admission the patient had experienced anorexia, nausea, and occasional vomiting. Some of his family also had had gastroenteritis during this period. He had no fever or chills but had became increasingly weak.

The patient had had pneumonia as a child. A pilonidal cyst had been removed surgically. There was no history of tuberculosis, hypertension, or renal disease. The patient's twenty-eight year old brother had had diabetes since the age of sixteen. An uncle also had diabetes.

Physical examination revealed a temperature of 36.4°C., pulse 120, respirations 16 and blood pressure of 170/104 mm. Hg. The patient was described as a well developed, blind, pale man with puffy eyelids, in no distress. There was a mild decrease in the skin turgor. The pupils were irregular and fixed. There were bilateral lenticular opacities. The eyelids were edematous and there was excessive lacrimation. The right slera appeared hemorrhagic. There were no palpable lymph nodes. The lungs were clear to percussion and auscultation. The left border of cardiac dullness was in the fifth intercostal space in the midclavicular line. The sounds were of good quality and the rhythm was regular. No murmurs were audible. Examination of the abdomen revealed no abnormalities. No edema was present. Deep tendon reflexes were absent below the thighs and there was decreased sensation in the feet.

Laboratory data were as follows: the hemoglobin was 11.1 gm./100 ml. and the white blood cell count 12,300/cu. mm. with 1 basophil, 3 eosinophils, 72 polymorphonuclear leukocytes, 21 lymphocytes and 3 monocytes. The red blood cells were described as normochromic. The urine specific gravity was 1.012 and the pH was 6.0. There was 3-plus proteinuria; 10 to 12 red blood cells and 1 to 2 white blood cells were seen per high power field of centrifuged urinary sediment. Tests for sugar and acetone were negative. The cardiolipin reaction for syphilis was negative. The non-protein nitrogen was 48 mg./100 ml. and the fasting blood sugar was 149 mg./100 ml. The total serum protein value was 5.5 gm./100 ml. with 2.8 gm. of albumin and 2.7 gm. of globulin. The serum sodium was 146, potassium 3.7, CO_2 14.9 and chloride 121 mEq./L. The thymol turbidity test was 1.8 units and the serum bilirubin was less than 0.8 mg. per cent. Red blood cell corpuscular constants were within normal limits. A roentgenogram of the chest was within normal limits. An electrocardiogram showed incomplete right bundle branch block; the QRS interval was 0.10 seconds, and the rhythm was sinus tachycardia with a rate of 108.

The patient was given a diet containing 80 gm. of protein, 80 gm. of fat and 250 gm. of carbohydrate distributed 2/7 at breakfast, 2/7 at lunch, 2/7 at dinner and 1/7 at bedtime. Twenty-six units of lente insulin and 10 units of regular insulin were administered each morning. A fasting blood sugar on the second hospital day was 390 mg./100 ml. at which time there was 3-plus glycosuria. The fasting blood sugar on the fourth hospital day was 280 mg./100 ml. at which time there was 1-plus glycosuria. The daily glucosuria in the urine ranged from 3-plus to negative.

The morning following admission the patient's nausea disappeared and his vomiting was ascribed to epidemic gastroenteritis. A culture obtained from the conjunctivas yielded white and yellow staphylococci which were coagulase negative. The patient received 1 unit of blood by transfusion and was encouraged to be up and about as much as possible. The nonprotein nitrogen at the time of discharge was 42 mg./100 ml. His urinary output ranged from 1,100 to 2,300 cc. daily.

The patient's second admission to the hospital was from November 10 to November 30, 1957. He entered the hospital because of malaise of one week's duration. At this time he stated that although he had had slight swelling of his legs two and one-half years prior to admission, this had been controlled by a regimen of diet and oral diuretics. He had been free of edema until three months prior to admission when edema recurred and became a problem. He had also noted increasing numbness of his feet, legs and hands. His feet became extremely cold. One week prior to admission rhinorrhea had developed and he had had a sore throat associated with a maximum temperature of 100°F. He had remained in bed for three days and had felt better for forty-eight hours at which time myalgia and joint aches had developed. He had vomited most of what he ate for three days but had kept fluids down well. One evening shortly before admission he had become short of breath and had been relieved by sitting up. The patient's urine was negative to the Clinitest® reagent most of the time with only an occasional trace of glucose. He was being maintained on 24 units of crystalline zinc insulin in the morning and 10 units before the evening meal.

Physical examination revealed a temperature of 37.5°C., pulse 80 and regular, respirations 18 and blood pressure 176/96 mm. Hg. The patient appeared to be in no acute distress. His weight of 150 pounds represented a 4 pound weight gain since his previous hospital admission. The conjunctival vessels in the right eye were injected. There was much edema about the eyes. There was 2 to 3-plus pitting edema from the feet to the knees, but no presacral edema. The pedal pulses were not palpable but the femoral pulses were strong. The deep tendon reflexes were absent in the legs and slightly diminished in the upper extremities. Position sense was absent in two toes and diminished in the thumbs. Bilateral mature cataracts were present and the right anterior chamber of the eye appeared "steamy" with punctate white precipitates on the lower portion of the cornea. Ocular tension on the right was greater than on the left. Bilateral slight arcus senilis was present. There were no other changes from the previous physical examination.

Laboratory data were as follows: The hemoglobin was 7.6 gm./100 ml. the red blood cell count was 2.44 million/cu. mm. and the packed cell volume was 27 per cent. The white blood cell count was 14,200/cu. mm. with 1 eosinophil, 5 bands, 73 polymorphonuclear leukocytes, 14 lymphocytes, and 7 monocytes. The urine specific gravity was 1.005 and the pH was 5.3; 3-plus proteinuria was present. The urine was negative for sugar and acetone; 13 to 17 white blood cells per high power field, an occasional hyalin cast, and finely granular and coarsely granular casts were present in the centrifuged urinary sediment. The stool was positive to both the guaiac and the benzidine reactions. The mean corpuscular volume was 110 cubic microns, and the mean corpuscular hemoglobin concentration was 28 per cent. The venous pressure was 67 mm. of saline and the circulation time was thirteen seconds (Decholin®). The non-protein nitrogen was 42, the fasting blood sugar 214, the serum uric acid 3.4 and the blood urea nitrogen was 30 mg./100 ml. The total serum protein value was 6.1 gm./100 ml. with an albumin/globulin of 3.4/2.7. The alkaline phosphatase was 2.7 Bodansky units, and the serum cholesterol level was 253 mg./100 ml. The serum sodium was 120, potassium 2.4, chloride 88 and CO_2 15.7 mEq./L. A roentgenogram of the chest showed slight pleural effusion on the left and bilateral lower lobe pulmonary infiltrates which were interpreted as pneumonitis. Films of the abdomen demonstrated displacement of normal gas shadows of the pelvis suggesting a mass in the right pelvis. An

electrocardiogram showed left ventricular enlargement, sinus tachycardia, and the QRS interval was 0.08 second. The cephalin-cholesterol flocculation test was 1-plus and the thymol turbidity test and total bilirubin were within normal limits. A culture of secretion from the eye yielded a heavy growth of coagulase positive hemolytic yellow staphylococci and a few coliform bacilli. The creatinine clearance was 31 ml./minute.

The patient was given an 1,800 calorie diabetic diet and received 24 units of crystalline zinc insulin before breakfast and 10 units before supper. The urine glucose varied from negative to trace. The blood pressure stabilized in the range of 130–150/80–100 mm. Hg. On the second, fourth, and fifth hospital days the patient's temperature reached 38°C. The white blood cell count rose to 18,400/cu. mm. with a shift to younger forms. The patient was treated with streptomycin and penicillin administered intramuscularly; and later with erythromycin. He remained afebrile thereafter.

The patient was given a transfusion of 3 units of blood and the hemoglobin rose to 11.5 gm./100 ml. The creatinine clearance decreased to 21.4 mg./minute. The patient's weight declined 10 pounds during the first four days of hospitalization. During the last seven days of hospitalization he received 1 gm. of Diamox® daily, without further decline in his weight. At the time of discharge, the blood urea nitrogen was 49 mg. per cent. A second stool was positive to both the guaiac and benzidine tests.

The patient's third admission to the hospital was from December 23 to December 24, 1957. In the three week interim, the patient did poorly. His appetite was poor, he continued to be weak and he lost weight. He complained of dyspnea. Two to three days prior to admission vomiting and diarrhea developed. The vomitus was described as coffee-ground in appearance but no red blood was observed. The urinary output was scant and was negative for sugar until the morning of admission, when it was 1-plus. The stools were described as being green and without blood.

Physical examination revealed a temperature of 36.2°C., pulse 106, respirations 22, and blood pressure 130/80 mm. Hg. The patient showed marked evidence of weight loss and was lethargic but responded readily to questioning. Examination of the heart and lungs was within normal limits. There were no palpable abdominal organs or masses. The skin was dry with decreased turgor. No edema of the extremities was present.

Laboratory data were as follows: the hemoglobin was 10.9 gm./100 ml. and the white blood count was 49,000/cu. mm. with 19 band forms, 69 polymorphonuclear leukocytes, 7 lymphocytes and 5 monocytes. The urinalysis on admission was positive for sugar and negative for acetone.

When seen five hours after admission the patient's condition appeared unchanged. Seven hours after admission the respiratory rate had increased to 36/minute and the blood pressure had dropped to 80/60 mm. Hg. The patient was moaning and confused and his peripheral pulses were weak. The nail beds appeared cyanotic. The patient was treated with intravenous fluids containing glucose, water, saline, and Vasoxyl.® The serum acetone was negative at this time. No urine was obtained after the admission specimen. The patient continued to be hypotensive without signs of congestive heart failure, sweating or tachycardia. He continued to be tachypneic and was noted to be incontinent of urine. He died fifteen hours after admission.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: This patient was found to have diabetes at the age of nine. He died twenty-eight years later, at the age of thirty-seven, with many of the complications of this disease. Dr. Humphrey, would you show us the roentgenograms at this time?

DR. HARVEY A. HUMPHREY: On the second hospital admission, routine chest examinations showed the heart to be normal. The first roentgenologic abnormality evident was bilateral pulmonary infiltration predominantly in the lower lobes and a collection of fluid in the left pleural space. This did not look like heart failure and one would suspect from the presence of the fluid, plus this infiltration, that this might have represented lymphangitic metastases. On the film of the abdomen, a mass was visible on the right side. There was some encroachment on the lumen of the bowel which also makes one suspicious of carcinoma in the pelvis, either primary or possibly metastatic. Follow-up examinations one week later showed no change. The bones appeared demineralized which would not have been unusual in a patient with diabetes of this duration.

DR. REINHARD: This patient had a twenty-eight year old brother in whom diabetes devel-

oped at the age of sixteen. He also had a diabetic uncle. The role of an hereditary factor in diabetes seems certain. However, we are particularly interested in the nature of this inheritance and in its manifestations in the juvenile as well as the adult type of diabetes. Dr. Alexander would you discuss this?

DR. FRANCE ALEXANDER: Dr. Reinhard, the evidence for an hereditary mechanism in diabetes comes largely from studies of diabetic pedigrees (such studies involving over 1,000 patients) and the coincidental occurrence of diabetes in monozygotic twins. The exact mode of transmission is not understood and is complicated by disparity between the genotype and the phenotype. This disparity is due to the variability in the age of onset and the severity of expression; the two general types, as you mentioned, being the juvenile severe diabetes and the adult form with late onset and mild expression. Utilizing these studies, and with these reservations in mind, it can be appreciated that it is very difficult to satisfy theoretical genetic ratios. However, the general pattern of a recessive mechanism emerges from most of the studies. Certain groups have expressed the opinion that this is a dominant trait with only a 10 per cent penetrance; others believe that there is a different genetic mechanism, a recessive one for the early onset, severe diabetes, compared to the late onset, mild type, which is dominant. Some workers regard the late onset, mild diabetes, as a manifestation of a heterozygous form of the recessive, that the early onset, severe diabetes, is the homozygous form. However, I think the important generalization from all the pedigree studies is that the theoretical inheritance ratios agree most closely with a single recessive mode of inheritance. There are several other facts which emerge from these studies which give additional evidence for this recessive type of linkage. There is no good evidence for sex linkage in these studies; however, there is a very definite possibility of increased consanguinity among parents of diabetic patients; lastly, the mean age of onset is not affected by the presence of diabetes in parents. The incidence of diabetes in siblings of one or more diabetic parents is greater than when neither parent is diabetic; if neither parent is diabetic the incidence is about 5 per cent; with one diabetic parent it increases to 11 per cent and with two parents diabetic the incidence rises to 16 per cent. The total incidence of diabetes is 5 per cent but this figure includes those that are not diagnosed and the potentials. The true incidence of the diagnosed diabetic subjects, is only 1 per cent leaving 4 per cent unaccounted for; this 4 per cent complicates all the genetic studies.

DR. REINHARD: Dr. Daughaday, is there anything known about what it is that is inherited in diabetes?

DR. WILLIAM DAUGHADAY: The underlying mechanism of diabetes is still completely unknown. The almost universal finding of very few beta granules and practically no extractable insulin in cases of juvenile diabetes would indicate that at least in this form of the disease the primary inheritance seems to be an inadequacy in the islet cells. In the older diabetic subjects this is probably not true because about one-third of the adult diabetic persons have essentially normal amounts of pancreatic insulin and beta granules.

DR. REINHARD: Dr. Wohltmann, I wonder if you would outline for us some characteristics of childhood diabetes from the point of view of its natural history?

DR. HULDA WOHLTMANN: The natural course of juvenile diabetes has been described by Dr. Hartmann based on the study of approximately 400 diabetic subjects.

At the onset of diabetes the disease may progress slowly, but if untreated, it progresses rapidly in severity so that the glucose/insulin ratio is in the range of 1.5 to 2.0. We make use of the glucose/insulin ratio which is determined by subtracting the urinary glucose lost in twenty-four hours from the total available glucose in the child's diet. This gives the number of grams of carbohydrate metabolized that day. This divided by the number of units of insulin administered gives the apparent metabolic glucose over insulin ratio.

Following regulation, there is a tendency for the child to regain tolerance or make endogenous insulin and the exogenous insulin is continually cut. In about one of every ten new diabetic subjects no exogenous insulin is needed for a period of time. Tolerance is again lost and then there is a succession of rapid and sometimes severe loss of tolerance followed by slower partial recovery until they have permanent severe diabetes. After a child has had the disease for three or four years the glucose/insulin ratios are not above 8 or 10, or lower than 2, with the majority about 4. In the individual child this varies very little from day to day.

Loss of tolerance may be seen when a child is getting insufficient insulin and is constantly hyperglycemic and glycosuric, when a child has an infection, severe emotional upset, too little exercise or too large a dose of insulin.

DR. REINHARD: Dr. Recant, another important problem would seem to be the degree of control of the diabetes in relation to the later development of diabetic complications. Unfortunately we know nothing about the severity of this patient's diabetes during childhood, and all we can say about the severity of his disease during later years is that he never took more than 45 units of insulin daily. Would you comment on the present evidence pertaining to the correlations between control of diabetes and the frequency and severity of complications.

DR. LILLIAN RECANT: There is very little doubt that in the diabetic subject the incidence of vascular-degenerative disease is tremendously increased over that in the non-diabetic subject. The major issue however concerns the nature of the factors that determine development of these degenerative complications. It has been shown that the duration of diabetes appears to be a major factor in the development of complications. White and Waskow studied 200 juvenile diabetic subjects similar to the patient under consideration today, with onset before age fifteen. These patients survived for more than twenty years and in these patients the authors found that 50 per cent showed evidence of nephropathy, 75 per cent showed calcified arteries and 80 per cent showed retinal disease. They commented that the appearance of these complications was not noted until the disease has been present for roughly ten years. There is little evidence linking the severity of diabetes with the development of complications. This may relate to the difficulty in defining severity. Is the amount of insulin required the determining factor or is the rapid development of ketosis on insulin withdrawal a determining factor? Because this has not been clearly established one can draw few conclusions. Now, with regard to the question of the control of diabetes and development of complications, much data are available. However a problem arises which relates to the definition of control. We see a patient perhaps once a month, or once every six months, and we compile a series of observations and conclude that the patient is either a well controlled or poorly controlled diabetic. We use the recurrent development of acidosis as evidence. But in general we can only make broad general categories describing the degree of control. In Dolger's study of over fifty-five juvenile diabetic subjects, seen over a long period of time, he found that there was no evidence of retinopathy unless the disease had existed for ten years or more. No difference in the development of this complication, regardless of the degree of control was noted. Bell says also that vascular disease develops only in relation to duration of the disease rather than to the state of control. Wilder comments similarly on retinopathy as does Henderson for renal disease. There is certainly then, a large school which believes that duration of disease is more important. However, on the other side of the question there is a formidable group including Jackson at Missouri, Hartmann's group here as well as Priscilla White and Joslin. They have found in their series that there is an excellent correlation between the development of all of the vascular complications and the degree of diabetic control. It is of note, however, that even in Root's group of the most poorly controlled diabetic subjects there were a quarter of them who were completely free of retinopathy, for example, after ten years of poor control. This is not then a simple question and there is not a simple answer. The present facts would appear to indicate that the degree of control may play some part but that the duration of the disease plays the major part in the development of complications.

DR. REINHARD: Dr. Wohltmann, a study has been made on children with diabetes followed in the diabetic clinic of the St. Louis Children's Hospital. An attempt has been made to determine if these children who have been poorly controlled had a higher incidence of complications later in life. Would you summarize this data?

DR. WOHLTMANN: Between the years 1922 and 1943 there were 180 patients with juvenile diabetes seen and it was believed that a study of these patients would be very worthwhile since this group had the unique characteristic that after they had their disease for some fifteen to twenty years they still would not be in an age group in which vascular disease was common. A follow-up study of these patients was carried out by Diesher, Daschner and Hartmann. There were only 120 whom they were able to contact. Twenty of this group lived too far away and did not return for any follow-up.

Thirty of this group died and the majority died during the first ten years of the insulin era. All the deaths in this group were due to acidosis and for the most part had occurred elsewhere. There were, of 120 patients, only 60 who returned. This group was divided up in terms of duration of diabetes, eleven to fifteen years, fifteen to twenty years and twenty to twenty-eight years. Of this group then, thirty were considered to be well controlled, and thirty were considered to be poorly controlled. Evaluating the group as a whole, one would conclude that the incidence of degenerative vascular disease appeared directly related to the duration of their diabetic life. This superficial evaluation would imply a poor prognosis for all diabetic persons. However, in the group of well controlled diabetic patients very little tendency to severe retinal disease was noted while a number of the poorly controlled patient's were blind or nearly blind. Renal changes and capillary fragility showed the same trend. In other words, the well controlled group showed very little change. We have very strong feelings that a child should be well controlled. Dr. Hartmann has one diabetic patient who has had diabetes for thirty-seven years and another for thirty-eight years; both of these patients are still in very good shape without any signs of complications. I think it is worthwhile to bring out one of the points which Dr. Recant discussed, namely, what is good control or poor control. We believe a child is excellently controlled if this child spills only 2 to 3 per cent of his total available glucose in the diet. We believe that the control is good with a spill of 5 per cent, fair with a spill from 5 to 10 per cent, and poor if the spill is greater than that. I also believe that you cannot evaluate control just by looking at a record or getting a blood sugar determination once a month or once every couple months. We ask the parents to check all urine specimens possible and to record results. The urines are checked by the Sheftel method so that we know exactly the grams of glucose spilled and by knowing the intake in the diet then we know the grams of glucose metabolised in a twenty-four hour period and can compute the G/I ratio. We are of the opinion that if we have this record on a day to day basis, we have a better chance of deciding what type of control these children have.

DR. REINHARD: Dr. Daughaday, I wonder if you could comment very briefly on prevailing theories concerning the pathogenesis of diabetic complications?

DR. DAUGHADAY: This is a terribly important problem and everyone in this field feels a need for a rational explanation for these complications. First of all, it is perhaps unwise to talk about all complications. There are complications which seem to be purely capillary disturbances as in the retina and in the kidney. These go together very nicely clinically and perhaps are of a single etiology. Then we have the complications of diabetic neuropathy which includes a number of syndromes. Some are apparently due to vascular disease whereas others seem to be actually a metabolic disease of the nervous tissue. There are certain types of neuropathy which correlate directly with acute episodes of poor control and respond nicely to correction of the diabetes. Theoretically we can prevent this type. Then of course we have the atherosclerotic problem which is only aggravated in the diabetic patient but represents the same underlying disease process seen in non-diabetic subjects, which I personally think is connected with lipid metabolism.

Concentrating on the capillary disturbance in the retina, kidney, and perhaps in other vascular areas, ideas concerning etiology can be grouped into three categories. First, some have suggested that actually the fluctuation in blood sugar may be important in this disease and that no diabetic person really has a normal blood sugar over most of the twenty-four-hour period and this produces changes in intracellular fluid which in some way damages the capillary tissue and produces the changes. Second, there is a growing body of evidence which suggests that one of the most characteristic changes is a disturbance in mucopolysaccharide metabolism. Insulin lack in skin has been shown to have a very definite effect on chondroitin sulfate, and hyaluronic acid metabolism. Extension of this approach to metabolism of chondroitin sulfate and hyaluronic acid in vascular tissue of diabetic subjects is needed. Actually the serum of diabetic patients with complications contains increased amounts of mucopolysaccharides although the intrepretation of this is very difficult. Lastly, the role of the adrenal and other endocrine factors in the etiology of diabetic complications has been emphasized. Dr. Becker has shown that administration of cortisone can aggravate experimental retinal lesions of diabetes and there is clinical evidence that administration of this drug can produce diabetic-type complications in the kidney. The increased incidence of retinopathy during pregnancy may

be related to increased steroid levels. There are suggestions that the pituitary is a contributing factor in the development of diabetic complications. One famous patient showed a complete remission of the retinal changes of diabetes following postpartum necrosis of the pituitary gland. Therapeutic adrenalectomy and hypophysectomy are not practical measures although theoretically reasonable. Most workers are quite discouraged with the risk of those procedures at the present time.

DR. REINHARD: Let us now take up the visual complications shown by the patient under discussion today. Dr. Becker, I wonder if you would start this discussion by telling us what one looks for in examining the eyes of any diabetic patient?

DR. BERNARD BECKER: Starting with the front of the eye, the first thing one usually sees is the change in the iris. For some unexplained reason, depigmentation of the iris develops in diabetic subjects. There is glycogen deposition in the pigment epithelium with rupture of cells and dispersion of pigment. This can be viewed by retroillumination of the eye or by slit lamp. Behind the iris, the lens is affected in diabetes in a number of ways. In the first place in acute diabetic episodes with marked acidosis, one can get a metabolic type of cataract. By slit lamp examination this can be distinguished from other types of cataract by the punctate appearance and the subcapsular location of the opacities. Later in life one may see senile cataracts in diabetic subjects, and there is evidence to indicate that these are actually more common in diabetic persons than in the normal population. The portion of the eye that we are usually most concerned with is the retina. With a dilated pupil and with careful examination, it is possible to detect some of the earliest capillary complications referred to by Dr. Daughaday. We can see the entire retinal circulation and visualize capillary aneurysms. We take such findings to indicate that vascular complications of diabetes are developing. As Dr. Daughaday indicated, at autopsy the retinal changes correlate well with the renal lesions. In fact, we believe this correlation to be even a closer one than is ordinarily expressed in the literature. Therefore it is our opinion that retinal capillary aneurysms when seen, indicate renal disease in terms of affected glomeruli. This glomerular disease may not be detected by any of our clinical tests. Renal function tests are not sensitive enough to pick up a few capillary aneurysms. The earliest stages of retinal vascular complications also correlate with some aspects of diabetic neuropathy. Recent studies by Fagerberg on biopsies of the sural nerve of diabetic patients demonstrate lesions in the capillaries of the nerve which resemble closely in staining characteristics and appearance those seen in the retina and in the glomerulus.

DR. REINHARD: Dr. Becker, we do not have very detailed information about the eye finding in this particular case. Unfortunately, this patient was never examined by an ophthalmologist. I wonder if you would comment on the probable cause of blindness in this particular case?

DR. BECKER: This patient was totally blind and had had diabetes for twenty-five years. The odds would be that he had advanced diabetic retinopathy which had progressed to the stage where he had hemorrhages into the vitreous. These organized, and in so doing, formed traction bands which detached the retina. I would anticipate complete retinal detachment, evidences of hemorrhage, and retinitis proliferans. In addition, it is common to find reaction in the anterior segment, such as new formed vessels on the surface of the iris, and secondary glaucoma. We are given the information in the history that this patient had a steamy cornea. When pressure goes up in the eye the cornea becomes steamy, so we know the patient had glaucoma. The patient also had cataracts and at this stage of the game, cataracts can develop just because of the inflammatory reaction in the eye and may have nothing to do with the original diabetic state.

DR. REINHARD: Let us now discuss the neurological disorder. At the time of his first admission to Barnes, this patient had no neurological symptoms but on examination the deep tendon reflexes were absent below the knees and there was some sensory loss in the feet. By the second admission he noted increasing numbness in the feet, legs and hands. His feet were very cold. The deep tendon reflexes were again absent in the legs and toe position sense was said to be absent. No neurological symptoms or signs were described with the third hospital admission which was only for a period of fifteen hours. Dr. Rosenbaum, are these findings compatible with the usual type of diabetic neuropathy?

DR. HERBERT ROSENBAUM: This man had the classic findings which we associate with diabetes. The neurologic complications are thought to be secondary to involvement of the nutrient

vessels. Segerberg showed that in cases of diabetic neuropathy 90 per cent of patients also showed retinopathy and kidney damage. In terms of the specificity of the disease it was his belief that older diabetic persons differ from juvenile diabetic persons in that in older patients we are dealing with both the usual aging process of arteriosclerosis and with the more specific changes in mucopolysaccharide. I do not believe that this man had any evidence of neurologic complications for a long enough duration to show the encephalopathy which frequently produces the personality changes associated with poor control of diabetes. This is seen to occur apart from peripheral polyneuritis or the more usual mononeuritis which may manifest itself in the production of pain long before any objective neurologic findings occur. A word about therapy. We have no specific therapy for diabetic neuritis. In the past, treatment was instituted with crude liver injections and/or vitamin B_{12}. I think that the institution of physical therapeutic measures are most important to increase blood flow and reduce edema.

DR. REINHARD: Dr. Daughaday, do you have anything to add regarding pathogenesis?

DR. DAUGHADAY: Yes, I would like to reemphasize the multiplicity of syndromes called diabetic neuropathy. I do not believe that 90 per cent of diabetic patients with neurological findings have either eye or renal disease. Neuropathy may occur early in the course of diabetes and may actually be present at the time of the first hospitalization long before retinopathy occurs. The vascular lesions that have been demonstrated in the nerves are very interesting but may not be present in all cases.

DR. REINHARD: Next I want to focus your attention on the discrepancy between the patient's blood sugar level and degree of glycosuria. During the second admission to the hospital the patient had no glycosuria at a time when the fasting blood sugar was 214 mg. per cent. At no time during the last hospital admission did the patient show more than 1-plus glycosuria. Dr. Bricker, would you comment on this?

DR. NEAL BRICKER: When the urine is free of glucose it may be assumed that all the filtered glucose is reabsorbed by the proximal tubule of each functioning nephron. The reabsorptive mechanism, which is an active one, is governed by an upper limit (Tm) and when the load of glucose exceeds this limit, glucose spills over in the urine. On the other hand when the load of glucose is less than the Tm level there is no glycosuria. In the normal human kidney, not all the nephrons reach their Tm simultaneously. Presumably this is due to some variation in the load to different nephrons which in turn results from a spread in infiltration rates among the population of nephrons. Consequently some spilling may occur from nephrons with high filtration rates before the absolute Tm is reached.

In explaining the paradox between blood sugar levels and glycosuria in Kimmelstiel-Wilson's disease, one must clearly distinguish I think between the plasma level of glucose and the filtered load. The load of glucose must be defined as the product of the plasma level and the glomerular filtration rate. If an individual nephron is reabsorbing maximally and if the load entering this nephron is just equal to the Tm there will be no glucose spilled. If the filtration of the nephron is cut in half however, doubling of the plasma level is required for the same amount of glucose to enter the nephron. This means then in practical terms that a patient with a glomerular lesion such as diabetic glomerulosclerosis, by having decreased permeability at the glomeruli with fairly normal glucose reabsorptive mechanisms in the tubules, may spill very little or no glucose at high blood sugar levels. In terms of management therefore one often has great difficulty in determining the insulin requirements of diabetic patients with Kimmelstiel-Wilson's disease on the basis of glucose excreted in the urine.

DR. REINHARD: An additional problem presented by this patient was marked edema, at a time when the venous pressure and circulation time were normal. The patient had variable, but in general, rather mild hypertension. There was persistent, rather pronounced proteinuria. Dr. Bricker, do you think this could be called a nephrotic syndrome?

DR. BRICKER: I think not, Dr. Reinhard, primarily because we cannot satisfy the criteria necessary to make this diagnosis. The most common causes of edema in the diabetic patient are of course heart failure and nephrosis and the nephrotic syndrome occurs in perhaps 10 per cent of patients with well developed Kimmelstiel-Wilson's disease. The only evidence in favor of the nephrotic syndrome in this patient is edema and proteinuria. Unfortunately we do not know the amount of protein excreted per twenty-four hours and we do not know if there were oval fat bodies in the urine. At the time of the second

admission the serum albumin level was normal and the cholesterol value was borderline.

DR. DAUGHADAY: One of the striking facts about the late stages of diabetes is the frequency of edema which cannot be attributed to the nephrotic syndrome or congestive heart failure. The albuminuria is often quite moderate, 2 or 3 gm. a day. I have attributed this disturbance to glomerular-tubular imbalance, somewhat similar functionally to that which we see in acute glomerulornephritis.

DR. REINHARD: Let us now consider the type of renal disease that this patient had. There are three main types of renal disease that one has to consider in diabetic patients; nephrosclerosis, pyelonephritis and Kimmelstiel-Wilson's disease. Dr. Sherry, do you think this patient had pyelonephritis? I would like you to comment briefly on why there is such a high incidence of this complication in patients with diabetes.

DR. SOL SHERRY: I cannot answer the question positively. I think there is a good chance that the patient had pyelonephritis, simply because autopsy statistics on patients with diabetes show an incidence of about 30 per cent. If one actually studies a large group of diabetic subjects at autopsy, the primary cause of death listed is acute pyelonephritis in some 7 per cent. The reason for a high incidence of pyelonephritis may be related to several factors. We find that women have pyelonephritis more often than men. This may be related to peroneal contamination. There is a tendency to infection in diabetic subjects possibly based on metabolic or vascular abnormalities. Glycosuria per se might enhance the growth of bacteria in the urinary tract. Many patients with diabetes have neuropathy with atonic bladders. This may lead to obstruction. Finally, many diabetic patients have infections in far distant sites which might serve as a focus for pyelonephritis.

DR. REINHARD: Dr. Harford, do you have any comments on resistance to infection in persons with diabetes?

DR. CARL HARFORD: It is well established that diabetic persons are subject to infection. For many years it was said that the increased level of blood sugar furnished a better culture medium for organisms. This view has been abandoned at the present time since experiments designed to test this hypothesis have not shown that serum with high levels of glucose support the growth of bacteria any better than normal serum. It has been found that in animals that are fasted for about thirty hours a greatly increased susceptibility to bacterial infection develops. In animals which are chronically starved this does not occur. Inasmuch as some ketosis might develop in this time, it is suspected that ketoacids may somehow alter the biochemical environment so that the organisms either are not killed by the bactericidal mechanisms of the body or are able to grow. There are also some experiments which point to a deficiency in the phagocytic mechanism in diabetes. In listening to the discussion here today I just wonder whether the capillary changes which have been discussed by several people might not have something to do with abnormal migration of phagocytes.

DR. REINHARD: Dr. Bricker, would you comment very briefly on whether or not this patient probably had Kimmelstiel-Wilson's disease?

DR. BRICKER: In addition to the retinal lesions, there are two findings in the diabetic patient which suggest Kimmelstiel-Wilson's disease. The first is the presence of oval fat bodies (and maltese crosses) in the urine. The second is the presence of normal sized or large kidneys in the presence of advanced renal insufficiency. We really do not have either of these observations in this patient and yet because of the long duration of his diabetes, because of the presence of an advanced nephropathy, and because of the absence of conclusive evidence for glomerulonephritis, I would think that the chances are overwhelmingly in favor of a nodular glomerulosclerotic lesion in many of the glomeruli.

DR. REINHARD: Dr. Moore would you comment on the anemia? Let us keep in mind that the patient had chronic azotemia for at least one year. He had indices suggesting hypochromia. The stool was guaiac positive and coffee-ground vomitus was observed.

DR. CARL V. MOORE: The lesion which caused the gastrointestinal bleeding is probably the one that caused this man's death. He certainly had a hypochromic anemia with bleeding from the gastrointestinal tract. He had diarrhea and I think he probably did have a lesion in the gastrointestinal tract. I am at a loss to place the lesion. We cannot ignore the roentgenological interpretation of a mass in the lower right quadrant, but that is hard to fit with the questionable history of vomiting coffee-ground material. His degree of azotemia was hardly enough to justify the suspicion of uremic ulcers in the gastrointestinal tract. One might suspect that

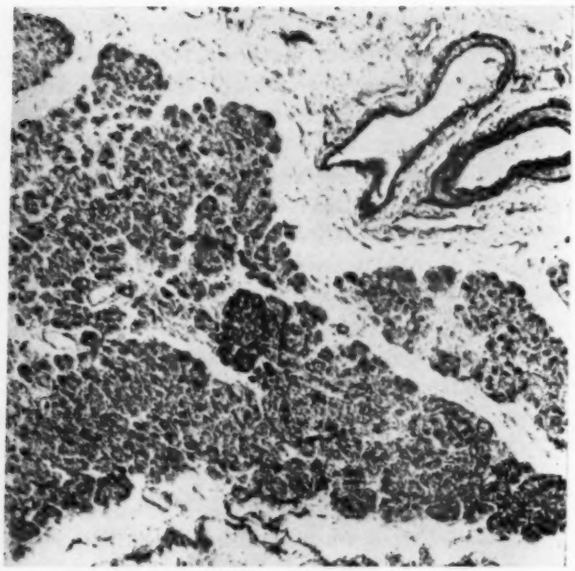

FIG. 1. A portion of pancreas showing the only islet of Langerhans that was found in nine sections. Aldehyde fuchsin × 50.

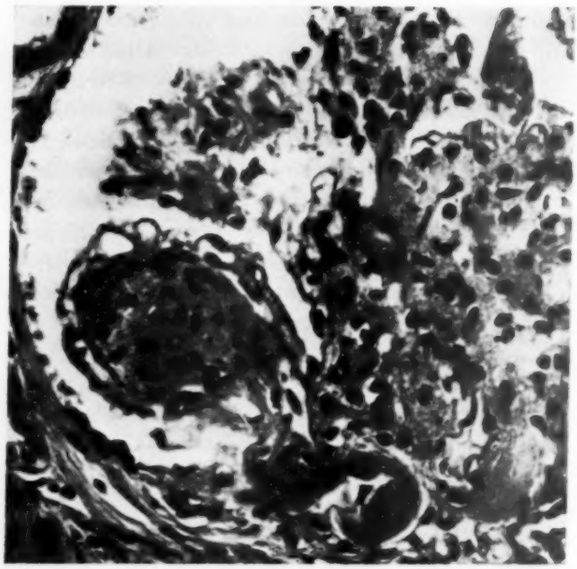

FIG. 2. A glomerulus showing a nodular lesion characteristic of intercapillary glomerulosclerosis. Hematoxylin and eosin × 300.

he had a carcinoma in the stomach with metastases to the lower peritoneum to account for the mass in the lower right quadrant, but he is mighty young for that and did not have any other symptoms to go along with it. I suppose an outside possibility would be that he had a lymphoma which involved both the peritoneum and the gastrointestinal tract. There is no evidence to indicate that he had an infection in the intestinal tract. It seems to me that he unquestionably will have a specific lesion here of great importance in his terminal episode.

DR. REINHARD: Dr. Moore has discussed the major possibilities in the terminal episode. The final diagnosis appears to me to be diabetes mellitus complicated by cataracts, retinal detachment and blindness; generalized arteriosclerosis including coronary sclerosis with incomplete bundle branch block; diabetic neuropathy; renal disease most likely due to a combination of nephrosclerosis, pyelonephritis and Kimmelstiel-Wilson's disease and finally carcinoma, site unknown.

PATHOLOGICAL DISCUSSION

DR. WILBUR A. THOMAS: This thin man with bilateral cataracts had 50 ml. of serous fluid in each pleural cavity and 600 ml. in the abdomen. The heart was hypertrophied weighing 450 gm. and the coronaries were markedly atherosclerotic (as were the aorta and other arteries) but no occlusions nor infarcts were noted. The lungs were slightly congested and edematous but otherwise normal. The spleen and liver showed only slight congestion and the brain and peripheral nerves were within normal limits.

The pancreas was small weighing only 40 gm. and on microscopic examination showed virtual absence of islets of Langerhans. Only one was found in nine sections (Fig. 1) but this one appeared to be normal.

The kidneys were of normal weight (180 gm. each) but the surfaces were finely granular and the glomeruli appeared prominent on gross inspection. Microscopic study showed fibrosis of almost every glomerulus with many having the nodular appearance characteristic of intercapillary glomerulosclerosis. (Fig. 2.) Some tubules contained neutrophils indicating focal acute pyelonephritis (Fig. 3) and in addition there was evidence for chronic pyelonephritis and arteriolar sclerosis. The eyes showed a variety of changes associated with diabetic retinopathy (Fig. 4) and will be described in detail by Dr. Becker.

The immediate cause of death appeared to be acute infection of the colon. Numerous, small superficial ulcers were found throughout the large intestine. These were cultured at the time of autopsy and Proteous mirabilis was identified. Microscopic examination of the ulcers showed

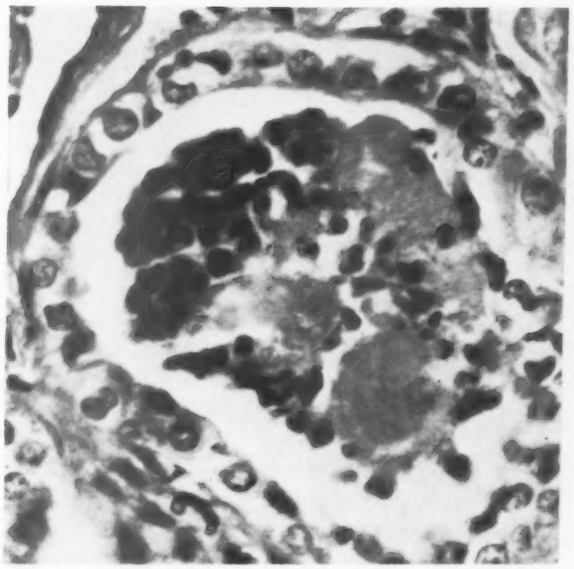

FIG. 3. A renal tubule containing a cast partially composed of neutrophils. Hematoxylin and eosin × 500.

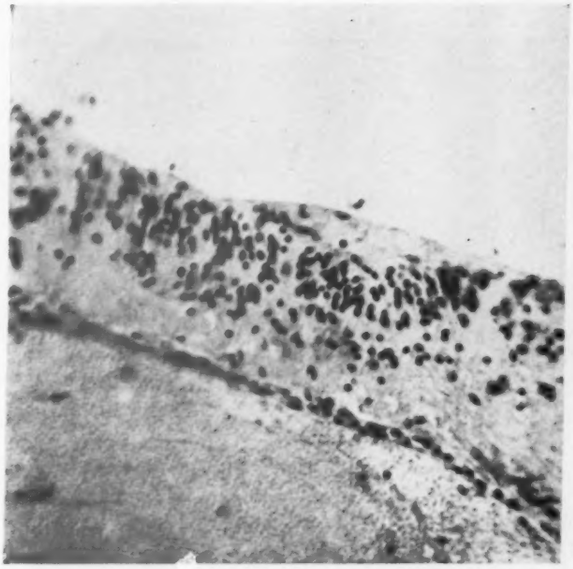

FIG. 4. A portion of degenerated detached retina with exudate beneath. Hematoxylin and eosin × 125.

necrosis of the mucosa with infiltration beneath by large numbers of neutrophils.

DR. BERNARD BECKER: It was apparent that the retina is detached with underlying eosinophilic subretinal fluid. The retina is pulled up behind the lens by retinitis poliferans originating from the disc. This is the sort of end result one gets after repeated hemorrhages into the vitreous, fibrovascular proliferation and the traction of the retina. This patient had glaucoma with the angle of the anterior chamber obstructed by adhesions of the iris to the cornea. The rise in intraocular pressure caused the corneal edema described.

Final Anatomical Diagnosis. Atrophy and fibrosis of pancreas with virtual absence of islets of Langerhans; intercapillary glomerulosclerosis; focal acute, and diffuse chronic pyelonephritis; degenerative changes in retina and optic nerve with subretinal hemorrhage, retinal detachment, perivasculitis, endopthalmitis, hemosiderosis and pannus degeneration; arteriosclerosis of aorta and coronaries, advanced; of splenic, renal and mesenteric arteries, moderate; hypertrophy of heart (450 gm.); multiple acute ulcers of the colon* (Proteus mirabilis cultured at autopsy).

*BERGE, K. C., SPRAGUE, R. G. and BENNETT, W. A. The intestinal tract in diabetic diarrhea. *Diabetes*, 5: 289, 1956.

Case Reports

Wegener's Granulomatosis*

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Portland, Oregon

"WEGENER'S granulomatosis" is a rare fatal syndrome of unknown cause, described by Klinger in 1931 and by Wegener in 1936, characterized pathologically by necrotizing granulomas of the respiratory system, focal necrotizing vasculitis and focal glomerulonephritis, usually terminating in uremia. In the respiratory tract the disease may produce severe sinusitis, destructive rhinitis (sometimes leading to saddle nose and orbital involvement), otitis, or ulcerative lesions of the oropharynx, larynx and tracheobronchial tree. In addition, or as the sole respiratory manifestation, there may be one or more large inflammatory masses in the lungs, which sometimes cavitate [*1*]. The vasculitis affects both arteries and veins and may result in widespread manifestations referable to the skin, joints, heart, spleen, parotid or prostate glands, or elsewhere, which are often transitory or recurrent in nature. The signs of renal damage appear midway or late in the course of the disease and death ensues after an average of six months from the onset of symptoms. Death often occurs in one to three months, but a few patients have shown more intermittent and less acute symptoms, and have lived two years or more.

The disease has no predilection for men or women, but more frequently appears in the fourth or fifth decades, in patients previously well, usually without allergic tendencies. The first evidence may be an intractable sinusitis or otitis, or perhaps cough, hemoptysis or chest pain may lead to the discovery of nodular or diffuse infiltrations in one or both lungs. Fever, joint pains, weight loss and weakness are commonly present, and may overshadow the respiratory tract involvement. If skin lesions are seen, they tend to be hemorrhagic or vesicular. Anemia, leukocytosis (occasionally with eosinophilia) and a rapid erythrocyte sedimentation rate are usually found. Antibiotic therapy has no apparent affect except on associated secondary infection. Treatment with steroids seems to ameliorate some of the symptoms, without significantly affecting the renal lesions or the eventual fatal outcome.

The rarity of this disease, and the challenging problems in pathogenesis which it presents, induced us to report herewith two cases from private practice. The first of these patients died in 1951 after an illness of four months. He was recognized as having had Wegener's granulomatosis only in retrospect after our second case was diagnosed, when one of us (G. L. M.) suggested that the microsections obtained at his autopsy be reviewed.

CASE 1. The patient was a thirty-nine year old foreman in a lumber mill who had been well until about June 15, 1951, when fatigue and a nonproductive cough developed; he noted a gradual weight loss of about 20 pounds, and migratory joint pains, followed on approximately August 1, 1951 by night sweats and anorexia. He was said to have had a miniature chest roentgenogram taken in May, 1951, which was negative. He had had attacks of acute sinusitis in 1937 and 1946, which improved each time after nasal polypectomy. Recurrence of pain about the nose and eyes occurred about July 1, 1951 followed in mid-August by redness of the eyes, with discharge. Penicillin had been given intramuscularly nearly continuously since July, and chloramphenicol eye drops had been used from about August 18 on.

At the time of physical examination on August 24, 1951, the patient appeared to be a well developed and well nourished white man. Marked injection of the conjunctivas was present. He was deaf in the right ear, and there was moderate scarring of the right eardrum. There was marked deviation of the nasal septum to the left with ulceration of the anterior portion of the left inferior turbinate and marked mucosanguinous discharge. Several small shallow clean ulcers on the hard palate were evident. The chest showed impaired resonance over both apices, but no rales.

The blood picture was one of mild normocytic anemia, with a white blood count of 11,600 per cu.

* From the Department of Pathology, University of Oregon Medical School Hospitals, Portland, Oregon.

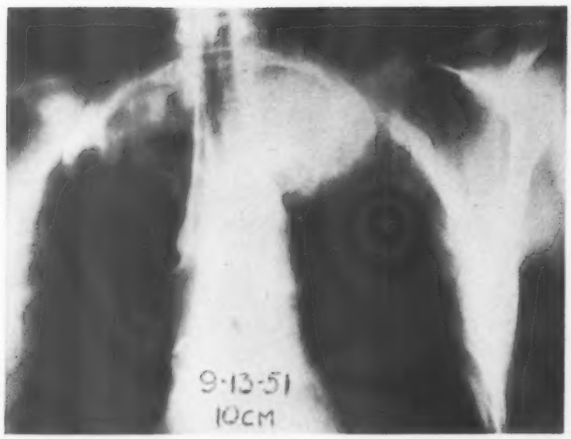

FIG. 1. Case 1. Body section radiogram 10 cm. from the back demonstrating a dense lesion at the left apex and nodular shadows at the right apex.

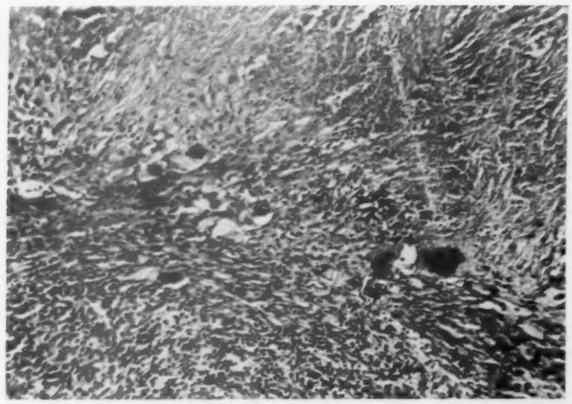

FIG. 2. Case 1. Photomicrograph of resected apical lung segment demonstrating caseation necrosis, epithelial cells, granulocytic exudate and fibrosis.

mm., of which 8 per cent were polymorphonuclear eosinophils, 6 per cent monocytes, and 2 per cent plasma cells. The erythrocyte sedimentation rate (Westergren) was 97 mm. in forty-five minutes. Urinalysis was negative. The sputum and gastric content were negative for tubercle bacilli by concentration and culture. The patient was hospitalized with the tentative diagnosis of moderately advanced pulmonary tuberculosis, chronic sinusitis, and conjunctivitis of undetermined type.

His temperature was elevated from 100° to 101°F. nearly every day through September 28, 1951, after which he was afebrile. Skin tests for tuberculosis with first and second strength PPD, and with histoplasmin and coccidioidin were negative. The serum protein determination showed 4 gm. of albumin and 3.5 gm. of globulin per 100 ml. of blood. Funduscopic examination on September 6 showed diffuse reddening of the choroid. At the upper outer margin of the left optic disc there was a small white elevated lesion. An ulceration of the left posterior tonsillar pillar had appeared. Several small tender left supraclavicular nodes were noted, but biopsy of these revealed no abnormalities. The ulcers of the nose and pharynx improved considerably during September while treatment with streptomycin and other antibiotics was being given. The ophthalmological consultant diagnosed "keratoconjunctivitis" and advised local treatment. The otolaryngologist reported hyperplastic purulent and polypoid pansinusitis. The roentgenogram of the chest showed large solid-appearing densities in either apex, better demonstrated on body section radiograms. (Fig. 1.)

On September 25, 1951 resection of a densely adherent apical-posterior segment of the upper lobe of the left lung was carried out. This specimen contained a soft yellow area of caseation necrosis, with radially arranged epithelioid cells around its periphery, and only occasional typical tubercles with giant cells. Focal masses of granulocytic exudate and a moderate amount of scarring were evident. The pathologist reported "active miliary and caseous tuberculosis." (Fig. 2.) However, special stains of the tissue for acid-fast bacilli were not made at this time, as the pathologist was under the erroneous impression that tubercle bacilli had been found in the sputum.

Therapy with paraminosalicylic acid was instituted, and the administration of streptomycin was continued. On September 29, 1951 the patient was confused intermittently. His tongue was red and swollen, and he was hoarse and had some difficulty swallowing. There was nausea and vomiting through October 3. On October 6, 1951 his urine showed 1 plus albumin, leukocytes and erythrocytes, and occasional hyaline casts. The blood urea nitrogen on October 8, 1951 was 19 mg. per cent. The blood count was about as before. Early on the morning of October 10, he was restless and complained of generalized aching with some diffuse abdominal pain and distention. Two days later there was aching in the groin and testicles. Physical examination, including neurological evaluation, showed only moderate abdominal distention and slight testicular swelling. Soon after midnight on October 13, following emesis, he began to complain of severe headache and pain in the neck, and a slight nuchal spasm developed. A petechial rash appeared on the chest and abdomen. The spinal fluid was grossly bloody but not under increased pressure. He soon lapsed into a deep coma and died several hours later.

At autopsy the apex of the right lung contained an irregular, discrete, friable, grayish yellow firm mass, 3 by 3 by 2 cm. in size, obliterating the pulmonary parenchyma and extending through the pleura to the chest wall. This had much the same microscopic appearance as the surgical specimen. The kidneys together weighed 610 gm. There were numerous minute red dots on the smooth, pale cortical surfaces. On section, the cortex averaged 10 mm. in thickness and was sharply demarcated from the apparently normal medullary tissue and pyramids. Microscopically, the

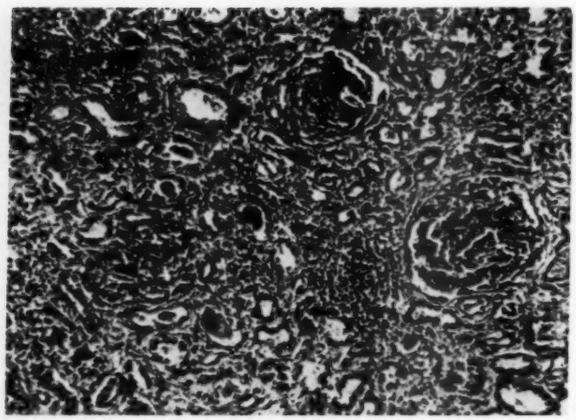

FIG. 3. Case I. Photomicrograph of kidney showing subacute glomerulonephritis. (Autopsy.)

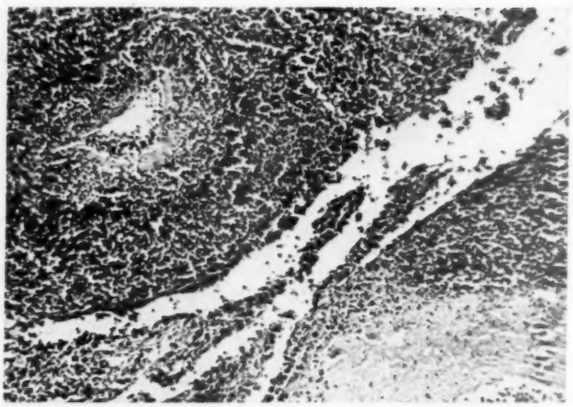

FIG. 4. Case I. Photomicrograph of testis showing arteritis. (Autopsy.)

picture of subacute glomerulonephritis was present, most of the glomeruli showing either hyalinization or epithelial and endothelial proliferation. There were numerous typical glomerular "crescents," secondary tubular changes, and some focal masses of granulocytic exudate associated with areas of necrosis in the cortex. (Fig. 3.)

Both testes contained irregular, patchy but discrete hemorrhages throughout. The parenchyma otherwise was soft and apparently normal. Microscopically, there were several foci of dense inflammation extensively involving medium-sized arteries. The arterial walls were markedly necrotic, and their lumens were practically filled with granulocytes. (Fig. 4.)

The brain weighed 1,530 gm. Extensive subarachnoid hemorrhage was present. About 150 ml. of blood was found in the posterior fossa. The cerebral vessels appeared normal on gross examination and no points of rupture or aneurysm were noted. The fourth ventricle was found to be filled with fresh blood, which extended upward through the cerebellopontine angles. Sections showed that the hemorrhage apparently arose in or near the choroid plexus, although there was some hemorrhage within the cerebellar substance as well. Focal acute granulocytic exudate with fibrin was present beneath the lining of the ventricle and in the choroid plexus. The meningeal membrane about the pituitary gland showed a chronic inflammatory process with focal necrosis and granulocytic exudate, some hemorrhage, a few large and quite bizarre multinucleated cells, and numerous scattered plasma cells and lymphocytes. The pituitary itself seemed relatively little affected.

CASE II. The second patient, R. V., a forty-six year old married lawyer and farmer, was admitted to Providence Hospital on December 27, 1955 with the chief complaints of hemoptysis of five day's duration; increasing weakness, nausea, vomiting; and dyspnea on slight exertion.

He had felt well until about May 1, 1955 when he awakened about 3:00 A.M. with an attack of "choking" and shortness of breath which lasted for three hours. This was followed by rather severe pleuritic pain in the left anterior midchest, radiating to the scapula, lasting one day, associated with malaise, dyspnea and fatigue. Thereafter he had occasional pleuritic twinges. Early in May a slightly productive cough developed. His sputum was blood-streaked in the morning during the first two weeks in July, 1955. There were also intermittent night sweats; slight loss of weight, strength, and appetite; low grade fever; and swelling and soreness of the left great toe and right fifth finger. About July, 1955, he began to have episodes of sharp aching pain in the left suprascapular region, which radiated to the left shoulder and upper part of arm and lasted two or three hours. These episodes occurred two or three times a week, especially after exertion.

The past history was not contributory. He had lived only in Indiana and in the Northwest. A roentgenogram of the chest taken in 1953 revealed no abnormalities.

Physical examination on July 18, 1955 was within normal limits except for impaired resonance in the right upper anterior chest without rales, and a small scaly lesion of the lower lip. Fluoroscopy and chest roentgenograms showed three rounded densities in the upper half of the right lung. (Fig. 5.) Except for a sedimentation rate of 100 mm. in one hour, routine laboratory work was normal, as were the blood uric acid, Paul-Bunnell heterophil agglutination test, agglutinations for typhoid and brucella, second strength PPD, and one sputum examination for acid-fast bacilli. Roentgenographic studies of the upper and lower gastrointestinal tract as well as an intravenous pyelogram were normal.

Bronchoscopy on July 10, 1955 showed moderate edema and redness of the upper lobe bar of the right lung with blood-tinged secretions coming from the orifice. Just below this, on the lateral wall of the right

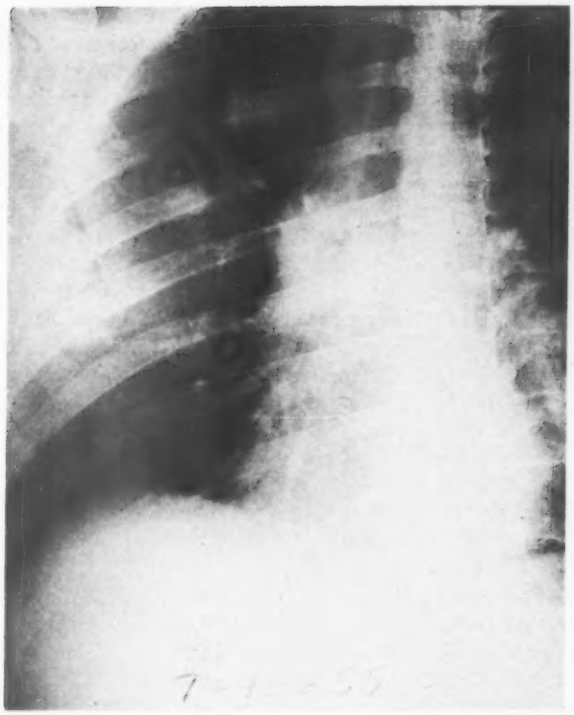

FIG. 5. Case II. Oblique projection demonstrating three rounded shadows in the right lung.

intermediate bronchus and projecting into the lumen for 2 or 3 mm., there was soft reddish granular tissue, from which a biopsy specimen was taken. The pathologist reported infiltration of the bronchial epithelium by lymphocytes and polymorphonuclear leukocytes.

Exploratory thoracotomy for biopsy of the pulmonary lesions was advised. The patient went to the Mayo Clinic late in July, 1955, where roentgenograms showed a small rounded shadow in the upper left lung as well as those in the right. A biopsy specimen of a right scalene node was negative. At thoracotomy on August 2, 1955, segmental resection of two of the masses in the upper right lung was carried out. Histopathologically, there were chronic granulomas (Fig. 6) which were sterile on culture for fungi, tubercle bacilli and brucella. The lesion on the lower right side of the lip was also removed and proved to be a grade 2 carcinoma.

The patient then felt improved until mid-September, 1955, when he began to note easy fatigue and malaise, and lost five pounds in weight. About September 20 a rather severe pain developed in the right sacroiliac region, which radiated to the right inguinal region, was unaffected by motion, and lasted two weeks. He also had two or three episodes of nausea, vomiting, headache and sour eructations. Physical examination in mid-October revealed no abnormalities except that some lower right quadrant tenderness was reported. Roentgenograms of the

FIG. 6. Case II. Photomicrograph of resected lesion in upper right lobe segment reported to be a "chronic granuloma."

hands and pelvis were not helpful, but that of the chest showed a rounded density 3 cm. in diameter in the anterior segment of the upper left lobe, and a similar density in the right mid-lung laterally. The 1:100 coccidioidin and histoplasmin skin tests were negative. A bone marrow study and blood protein determination were normal.

His blood count remained normal except for a 10 per cent monocyte count and an erythrocyte sedimentation rate (Westergren) of 95 mm. in forty-five minutes. The urine showed 1 plus albumin, 4 to 6 leukocytes and erythrocytes per high power field, and a few granular casts.

Therapy with prednisone was given for one month beginning in mid-October. This appeared to relieve his joint pains but his other symptoms continued and nausea became more frequent. Complete physical examination, including funduscopic examination, was within normal limits in mid-November.

The patient returned to the Mayo Clinic on November 30, 1955. At that time he had definite renal insufficiency. Albumin, casts, erythrocytes and leukocytes were found in the urine, the specific gravity of which was low. The blood count showed 9,500 white blood cells per cu. mm., with 67 per cent polymorphonuclear leukocytes, 11.5 per cent monocytes, and 7.5 per cent polymorphonuclear eosinophils. The blood urea nitrogen was 156 mg. per cent, and the creatinine 6.2 mg. per cent. The roentgenograms of the skull were reported to show some decalcification of the right anterior clinoid process along its inferior aspect. The chest roentgenogram showed a rounded shadow 1.5 cm. in diameter in the upper left lung and a residual density in the right mid-lung peripherally. A renal needle biopsy specimen demonstrated glomerulonephritis (Fig. 7).

The patient did poorly on his return home, and continuing weakness, nausea and vomiting, exertional dyspnea and hemoptysis led to his final hospitalization on December 27, 1955. The only significant

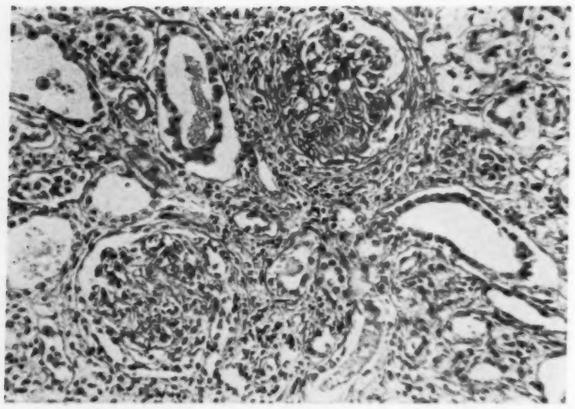

FIG. 7. Case II. Photomicrograph of renal needle biopsy specimen demonstrating glomerulonephritis. (Courtesy of Mayo Clinic.)

physical finding on this admission was the presence of subcrepitant rales over both lung bases posteriorly. His hemoglobin was 4.2 gm. per 100 ml. of blood with 1.78 million red blood cells per cu. mm. The erythrocyte sedimentation rate was 114 mm. in forty-five minutes. The white blood cells were normal, reticulocytes were 8.5 per cent, and the bone marrow showed only hyperplastic changes. The results of urinalysis were much as before. The roentgenogram of the chest showed extensive bilateral infiltrations (Fig. 8), attributed to uremia and perhaps in part to the aspiration of blood.

Sputum studies again were not helpful. The plasma contained 2.3 gm. of albumin and 4. 1 gm. of globulin per 100 ml. of blood. The gamma globulin was 22.8 mg. per cent. These plasma protein abnormalities persisted. The blood icterus index rose gradually to 15 units before his death, and the thymol turbidity and cephalin flocculation tests remained abnormal. The blood cholesterol and cholesterol esters rose to high levels (480 and 376 mg. per cent, respectively, in March, 1956). The blood urea nitrogen rose from 73.6 mg. per cent on admission to a high of 184 mg. per cent on January 13. It then fell sharply to 35 mg. per cent early in February, but terminally rose to 125 mg. per cent.

Initial treatment consisted of transfusions, administration of antibiotics, menadione bisulfite, antacids and a bland diet. For the first week in January, 1956, he complained of non-cramping pain in the abdomen, flank and lumbar regions, associated with some tenderness there and urgency of urination. Chlorpromazine was given but it had little effect on his increasing nausea, hiccoughs and vomiting. Therapy with corticotropin and prednisone was resumed on January 3, 1956.

By January 8 he required supplementary intravenous fluids. On January 12 he was drowsy and confused and had several convulsions. Surprisingly, after ten days in semi-coma, on January 23 he became more alert and was soon able to take a soft diet. On January 26 isolated weakness of all motions of the right shoulder developed, without sensory disturbance or abnormal reflexes, which improved after two weeks.

The urine culture of January 27 showed hemolytic staphylococcus aureus, sensitive to mycifradin, furadantin and bacitracin, but resistant to the usual antibiotics. Similar findings were reported on about a dozen occasions during the rest of his course. Furadantin and various antibiotics were administered with no appreciable effect. Treatment otherwise consisted of prednisone and corticotropin, transfusions from time to time, a low-sodium bland diet, and potassium chloride whenever indicated by low serum potassium levels in the electrolyte studies.

The chest roentgenogram of January 30, 1956 showed marked clearing of the diffuse bilateral infiltrations. The previously noted densities in the left apex and right mid-lung were now difficult to make out. (Fig. 9.) Subsequently roentgenograms showed little change.

A fine, maculopapular, reddish eruption developed on the posterior chest for several days in mid-January; this recurred and persisted early in February. He was usually afebrile, except for an elevation to 101.6°F. On January 3, 1956, on which date the urine was grossly bloody. He displayed palmar erythema and complained of intermittent muscular soreness and tenderness of the upper extremities and later of the legs. The muscular symptoms improved when the daily dose of prednisone was increased to 30 mg., but marked generalized muscular atrophy appeared. In mid-February he began to have persistent edema of the feet and ankles, and petechiae were noted on the dorsum of the feet. On March 1 a "splinter hemorrhage" near the superior temporal branch of the left retinal artery was noted on funduscopic examination. The liver edge was at the costal margin and was slightly tender. Inconstant crepitant rales were heard in the right base posteriorly. His blood pressure averaged about 170/110 mm. Hg.

The patient felt relatively comfortable in mid-March and was able to sit up several times a day. His urine output varied from 1,200 to 2,600 cc. a day, the larger amounts occurring every fourth or fifth day. Late in March, however, he exhibited a "moon facies," and his weight quickly rose from about 119 to 143 pounds. Edema extended upward to involve the lower extremities and abdomen. On March 31 a gallop heart rhythm developed, and a pericardial friction rub was heard. By April 9 dullness and bronchial breathing had appeared in the right base posteriorly. The liver edge was 2 fingerbreadths below the costal margin and the neck veins were moderately distended. Nausea continued, and diarrhea developed. Terminal temperature elevations to about 101°F. were reported. There were convulsions on April 24, and he died the following day.

The significant autopsy findings were limited to

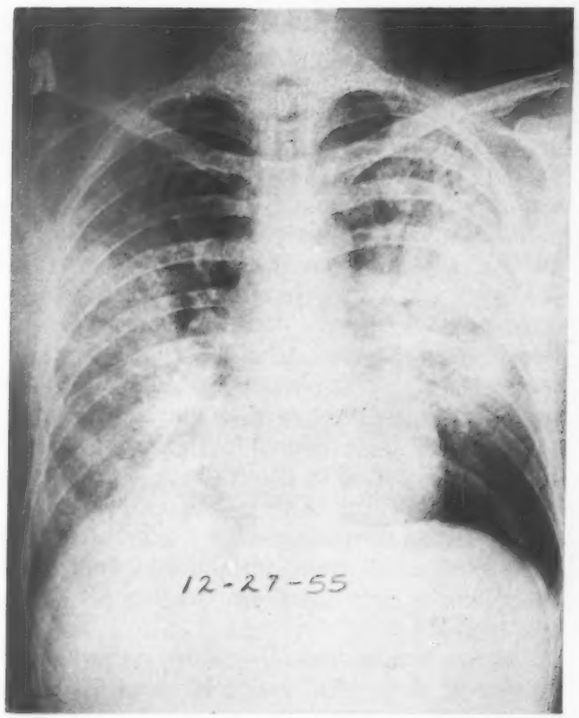

FIG. 8. Case II. Roentgenogram of chest taken during final hospital admission (December 27, 1955) demonstrating extensive bilateral shadows attributed to uremia.

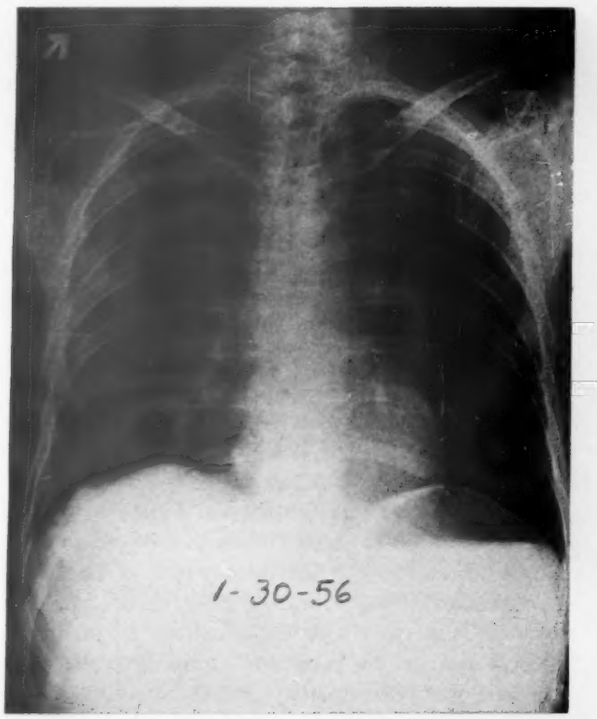

FIG. 9. Case II Chest roentgenogram taken on January 30, 1956 showing marked clearing of the diffuse bilateral densities.

the lungs, heart, brain, kidneys, esophagus and bladder. There were multiple firm nodular, yellowish gray areas up to 1.5 cm. in diameter in the right lung only, and these showed fibrocaseous necrosis with focal calcification. Stains for acid-fast organisms were negative. The heart showed a few small areas of acute suppurative exudate with necrosis of myocardial bundles and several endocardial thrombi of varying age.

The kidneys together weighed 470 gm. and on gross examination showed some thinning and granularity of the cortex. Microscopically there was severe generalized hyalinization and marked degeneration of both tubules and glomeruli. Some of the tubules were filled with necrotic debris and granulocytic exudate, and there was interstitial scarring. Although few typical glomerular crescents or demilunes were seen, the character and distribution of the process were quite similar to those present in glomerulonephritis.

The brain weighed 1,460 gm. and its surface showed several foci of acute hemorrhage over the right frontal pole and in the left parietal area. Some opacity and thickening of the pia-arachnoid was noted. There was a cystic, calcific, yellow, granular lesion 2.5 cm. in diameter in the right occipital lobe and a pink area of softening in the right parietal cortex, 1.5 cm. in diameter. Another circumscribed yellow 1.5 cm. lesion was noted in the posterolateral

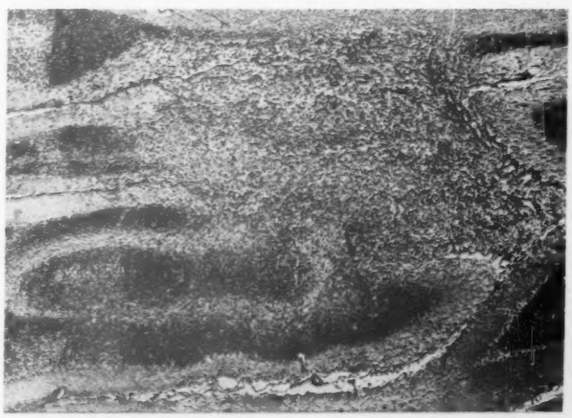

FIG. 10. Case II. Photomicrograph showing healing infarction of cerebellum.

portion of the left cerebellar hemisphere, lateral to the dentate nucleus. Microscopically, there were areas of acute granulocytic exudate involving the choroid plexus. There were several foci of suppuration in the brain as well as infarctions with hemorrhage of varying age. (Fig. 10.) Special stains were negative for microorganisms.

There was acute ulcerative inflammation of both the urinary bladder and the esophagus. Moderate acute and chronic passive congestion of the liver was evident.

COMMENTS

In 1954 Fahey and associates [*2*] summarized the findings in twenty-two cases of Wegener's granulomatosis collected from the literature, and added seven patients of their own. In the latter group the diagnosis was made from the clinical picture and following pulmonary resection in two patients; in the other five it was made only at autopsy. One of their patients lived forty-eight months; another, who was given steroids during most of his course, lived for thirty-nine months. Nitrogen mustard was given to this latter patient, and appeared to produce a brief remission. Since publication of this paper other reports [*3–5*] have appeared in the literature, bringing the total to thirty-five cases.

In the differential diagnosis, Fahey et al. list the following: (1) specific infectious granulomatous diseases; (2) sarcoidosis; (3) the rare progressive "granuloma gangrenescens" involving the nose and face, which is probably closely related to Wegener's granulomatosis although not ordinarily associated with either vascular or renal lesions; (4) polyarteritis nodosa; and (5) allergic granulomatosis and angiitis, such as may occur in patients who die of asthma [*6*]. Neuss [*7,8*] found 165 cases of granuloma gangrenescens reported in the world literature. He notes its histologic similarity to some forms of polyarteritis nodosa, its similar predilection for patients between the ages of twenty and forty years, and the same preponderance of males over females (a ratio of about 2.5 to 1 for both diseases). He holds that the term "Wegener's granulomatosis" should apply only to patients with granuloma gangrenescens and generalized polyarteritis. He also discusses a possible relation of granuloma gangrescens to sarcoidosis and disseminated lupus erythematosus.

Most authors agree that Wegener's granulomatosis should be considered a subgroup of polyarteritis nodosa with certain anatomical and clinical peculiarities. The reader is referred to the paper of Godman and Churg [*9*] for a detailed discussion of the comparative pathology of polyarteritis nodosa and related conditions and for an extensive bibliography. These authors note several features of Wegener's granulomatosis which differentiate it from the "microscopic form" of polyarteritis nodosa. In the former, there is the peculiar predominant and aggressive character of the necrotizing lesions in the respiratory tract, and renal involvement occurs with impressive regularity and severity. Tissue eosinophilia is not commonly found in Wegener's syndrome, and the clinical stigmas of allergy are usually absent. They comment on the "continuous spectrum of tissue changes from pure necrosis and granuloma formation to pure angiitis" in the various manifestations of polyarteritis and allergic angiitis and granulomatosis.

Fienberg [*10*] suggests that cases of this latter type be classified as "pathergic granulomatosis," from Kossle's term "pathergy," designating all morbid phenomena which can be produced by a state of altered reactivity. He conceives of disseminated and focal varieties, Wegener's granulomastosis representing the disseminated form. The focal form would include such phenomena as "idiopneumonic granulomatosis," some instances of cholesterol pneumonitis, and perhaps eosinophilic granuloma of the lung.

French and Civin [*11*] recently reported the case of a forty-two year old man dying of cholesterol pneumonitis, pulmonary granulomatosis and vasculitis, and glomerulonephritis. They consider this to be, perhaps, an intermediate stage between cholesterol pneumonia on the one hand and fullblown Wegener's granulomatosis on the other.

Edwards et al. [*12*] have recorded the findings in a twenty-five year old woman whose complaints were cough, hemoptysis, chills, malaise, arthralgia and hematuria. Extensive pulmonary infiltrations due to necrotizing alveolitis, glomerulonephritis, and necrotizing arteritis of the spleen were found. They considered a hypersensitivity reaction to be the basis of these changes. This case no doubt represents still another variant in the spectrum mentioned, but the absence of granulomatous lesions places it apart from Wegener's syndrome.

In our first case, death occurred from subarachnoid hemorrhage before the renal involvement had become clinically significant. To our knowledge this complication has not been previously reported in this syndrome. The patient had had lesions both in the upper respiratory tract and in the lungs, but the former were not as severe as most of those reported in the literature, and had improved during his first month of hospitalization.

An interesting feature of this case was the initial erroneous diagnosis of pulmonary tuberculosis by the pathologist on the basis of exam-

ination of both the excised segment of lung and the autopsy material, apparently due to the misunderstanding that acid-fast bacilli had been found in the sputum. We had been led to conclude that the negative tuberculin test placed the patient in the very small category of those with active tuberculosis and anergy to tuberculin, but we were disturbed by our inability to explain the arterial lesions in the testes and the spontaneous subarachnoid hemorrhage which caused his death. When Wegener's syndrome was diagnosed in our second case, it occurred to us to review the tissues in Case I. The pulmonary, vascular and renal lesions were correlated, and only then did the pieces of this puzzle fall into place.

In Case II there was clinical evidence of widespread involvement in addition to the respiratory and renal systems, namely of the joints, skin, peripheral nerves, muscles and liver. The diagnosis in this instance was made during life. The pulmonary and renal biopsy specimens obtained at the Mayo Clinic, while not diagnostic in themselves, provided evidence consistent with Wegener's granulomatosis. It is interesting that the patient showed marked but temporary improvement after his condition had been nearly fatal due to uremia early in January, 1956. Whether this was spontaneous or due to the steroid therapy which had been initiated a few days before his deterioration, it is difficult to say. The same applies to the roentgenologic improvement noted in the pulmonary lesions. We were of the opinion that steroid therapy had helped to relieve the arthritic symptoms early in the patient's course, and later the muscular soreness and tenderness, although it had no apparent affect on the generalized muscular atrophy, nor on the severe impairment of renal and liver function. The urinary tract infection with a resistant hemolytic staphylococcus aureus apparently did not contribute significantly to his renal failure and death.

Except for temporary weakness of the right shoulder girdle muscles, there were no localizing neurological findings, and his terminal convulsions were attributed to uremia. The cerebral involvement found at autopsy was unexpected.

In regard to the etiology and pathogenesis of Wegener's granulomatosis, we would agree with those who place it in the spectrum of disease patterns closely related to polyarteritis nodosa. The theory that Wegener's syndrome is a manifestation of hypersensitivity seems well-founded. Since the respiratory tract is presumably the primary site of involvement, the offending agent or agents are thought to enter through the respiratory tract, but what they are and how they produce such profound reactions in the blood vessels remains unexplained. Effective treatment of this disease must no doubt await a better understanding of hypersensitivity mechanisms generally.

SUMMARY

Wegener's granulomatosis is characterized by necrotizing granulomatous lesions of the upper respiratory tract and/or lungs, necrotizing vasculitis and focal glomerulonephritis, terminating usually in uremia.

Two additional cases are reported, bringing the total in the literature to thirty-seven. In Case I an initial erroneous diagnosis of tuberculosis was made histopathologically from the resected segment of lung and from autopsy material. Death was due to spontaneous subarachnoid hemorrhage complicating arteritis. This complication, and the cerebral lesions found at autopsy in Case II, have not hitherto been reported in this disease.

The spectrum formed by this and other conditions closely related to polyarteritis nodosa is discussed. A hypersensitivity mechanism has been inferred by most authors but its nature remains to be elucidated. Treatment of this disease so far has been unsatisfactory.

Acknowledgment: The authors gratefully acknowledge the kindness of the Mayo Clinic and of Dr. Jeff Minckler in making available the pathologic material in Case II, and the help of Dr. Howard P. Lewis, Professor of Medicine, University of Oregon Medical School, in the clinical diagnosis in this patient.

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Simultaneous Placental Transfer of Factors Responsible for L.E. Cell Formation and Thrombocytopenia*

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THE discovery of the L.E. cell by Hargraves in 1948 [*1*] has broadened the diagnostic armamentarium which can be used to differentiate systemic lupus erythematosus (S.L.E.) from a host of clinical disorders which this disease may simulate. In the past decade a considerable number of investigations have been conducted to elucidate the nature of this unique bio-assay phenomenon. Haserick [*2*] was the first to demonstrate that the factor responsible for the production of the L.E. cell resides only in the gamma globulin fraction of blood serum. These observations have recently been confirmed [*3,4*]. Haserick further has claimed that the L.E. factor is immunologically distinct from other gamma globulins [*5*].

Systemic lupus erythematosus may be associated with a host of serological disturbances which suggest the presence of extensive anomalies in protein metabolism. Among these one may include: hypergammaglobulinemia, false-positive serological tests for syphilis, circulating anticoagulants, and autoimmune hemolytic anemia. Miescher [*6*] has proposed that the L.E. factor is an antibody directed against cell nuclei. Recent work in other laboratories [*3,7*] has given support to this hypothesis.

Thrombocytopenia is a common complication of S.L.E. The frequent association of this condition with splenomegaly in S.L.E. has led to the general belief that this hematologic disorder results from hypersplenism. The more frequently associated finding of leukopenia would appear to lend some credence to this concept. In recent years Tullis [*8*] has pioneered investigations with regard to the presence of platelet antibodies in various thrombocytopenic syndromes. His studies have indicated the presence of platelet antibodies in the majority of patients with idiopathic thrombocytopenic purpura, hypersplenism and neonatal purpura. On the other hand, serums of patients with thrombocytopenia secondary to deficient platelet production (e.g., leukemia, metastatic bone disease, radiation) generally failed to reveal the presence of platelet antibodies. To support his finding is the generally favorable therapeutic effectiveness of corticosteroids in the diseases characterized by the presence of platelet antibodies in comparison with the refractoriness of the thrombocytopenia in the group with defective platelet production. In a small series of patients with S.L.E., Tullis [*9*] was able to demonstrate the presence of platelet antibodies in only one instance, the only one in addition to that recorded in the present report.

In this report an unusual observation is recorded which afforded an opportunity to study the problem of thrombocytopenia in S.L.E. Nature provided an *in vivo* "experiment" to observe in a newborn of a mother with S.L.E. and thrombocytopenia the possibility of passive placental transfer of related humoral factors present in this patient.

In a study of umbilical cord blood of two pregnant women with S.L.E., Bridge and Foley [*10*] were able to demonstrate the formation of L.E. cells by several technics. In one patient, reported in detail, the activity of cord blood was considerably less than the activity of the maternal blood. Examination of the child's blood for lupus activity seven weeks after birth revealed "indefinite findings." No studies were conducted in the interim. At four months there was no evidence of activity. These investigators were unable to demonstrate any inhibiting antibodies to the L.E. factor in the child's blood.

In a recent communication Berlyne et al. [*11*]

* From the medical service of the Beth-El Hospital, Brooklyn, New York. This investigation was supported by a grant (H-3397) from the U. S. Public Health Service.

reported two additional cases of placental transfer of L.E. factor. The presence of L.E. factor in these full-term infants could not be demonstrated after seven weeks of life. The children appeared to be entirely well at the age of six months.

In this study we are reporting another example of placental transfer of L.E. factor. For the time being this case is unique because thrombocytopenia developed in the mother with L.E. and she gave birth to a premature child with neonatal thrombocytopenia. An opportunity to conduct platelet antibody determinations in mother and child was available and the results are most interesting.

CASE REPORT

First Admission

This fifteen year old single, white female was admitted to the Beth-El Hospital on October 12, 1955 complaining of fever, diffuse joint pains and a facial rash of one week's duration. Her past history was non-contributory. On physical examination she appeared to be a well developed, well nourished female, appearing two or three years older than her stated age. The temperature was 103°F.; pulse, 100; respiration, 24; blood pressure, 120/82 mm. Hg. An erythematous eruption was evident over the bridge of the nose spreading out over both malar ridges. There were small ulcerations with areolae of deep erythema on the hard palate. Bilateral non-tender cervical adenopathy was present. The heart and lungs appeared normal. The abdomen was soft without enlargement of either liver or spleen. The extremities were normal. The neurological examination was within normal limits. The laboratory data disclosed hemoglobin, 10 gm. per cent; red blood cells, 2,500,000/cu. mm.; white blood cells, 2,000/cu. mm. with a differential of 56 per cent segmented polymorphonuclear, 6 non-segmented forms, 36 lymphocytes and 2 monocytes. The number of platelets present on the blood smear was adequate. Urinalysis revealed a specific gravity of 1.026; albumin, 1 plus; sugar, negative; 5 to 10 red blood cells and white blood cells in the centrifuged sediment. Blood sugar, 85 mg. per cent; blood urea nitrogen, 20 mg. per cent; total protein, 6.3 gm. per cent; albumin, 3.3 gm. per cent; globulin, 3.0 gm. per cent. Mazzini and Coombs' tests were negative. Repeated L.E. preparations were strongly positive. The chest roentgenogram and electrocardiogram were normal. The patient was treated with meticorten and there was a prompt defervescence of temperature, joint pains and malaise. The butterfly eruption gradually disappeared during the ensuing week. The dosage of meticorten was gradually decreased from 40 to 20 mg. per day and the patient was discharged asymptomatic on November 15, 1955.

The patient was followed regularly on an outpatient basis. In general she did very well on an average daily maintenance dose of 17.5 mg. meticorten. The stigmas of Cushing's syndrome quickly appeared as evidenced by a moon face, hirsutism, facial acne, extensive purplish striae and a ravenous appetite. L.E. cells could no longer be demonstrated. In late January, 1956, she became pregnant. She continued to take 15 to 20 mg. meticorten daily until July, 1956. At this time her pregnancy was progressing normally and she felt well. It was decided to decrease steroid therapy gradually. Over the ensuing month this medication was reduced to 5 mg. daily. She continued to do well until September, 1956, when periorbital and pedal edema developed despite a rigid low salt diet. The blood pressure was now 130/95 mm. Hg. Repeat L.E. preparations disclosed minimal activity. Blood chemical studies including sugar, blood urea nitrogen, proteins, and electrolytes were within normal limits. Urinalysis disclosed 1 to 2 plus proteinuria. By the end of September marked edema of the legs and face had developed. The blood pressure was 130/90 mm. Hg. Small ulcerations re-appeared on the hard palate associated with a faint erythematous blush over the breasts. Low grade fever was present.

Second Admission

The patient was readmitted on October 2, 1956 because of marked edema of the legs and soreness of the mouth. She had been taking only 5 mg. meticorten daily since August 1, 1956. On examination she appeared to be in moderate distress because of joint aches and edema. Moderate periorbital edema was present. The blood pressure was 130/90 mm. Hg; temperature, 100°F.; pulse, 90; respiration, 24. There were many purple striae over the abdomen, breasts, thighs and buttocks. Several cotton-wool exudates (cytoid bodies) were present in both optic fundi. There were many superficial yellowish ulcerations on the hard palate and buccal mucous membranes. Bilateral tender cervical adenopathy was present. The heart and lungs were normal. A gravid uterus with estimated thirty-four-week viable fetus in cephalic presentation was present. The liver and spleen were not palpable. There was marked edema of both legs extending upward to include the vulva. Laboratory data disclosed hemoglobin, 10.5 gm. per cent; white blood cells, 5,800/cu. mm. with a normal differential count. Urinalysis disclosed a specific gravity of 1.020; albumin, 4 plus; sugar, negative; 3 to 5 red blood cells and many white blood cells in the centrifuged sediment. The blood urea nitrogen was 22 mg. per cent; total protein, 4.2 gm. per cent; albumin, 1.6 gm. per cent; globulin, 2.6 gm. per cent; electrolytes, normal. The Mazzini test was negative. L.E. preparations were again strongly positive.

On October 6, 1956 she went into labor and spontaneously delivered a 3 pound 3 ounce (1.45 kg.) male child. On October 8, 1956 while doing an L.E.

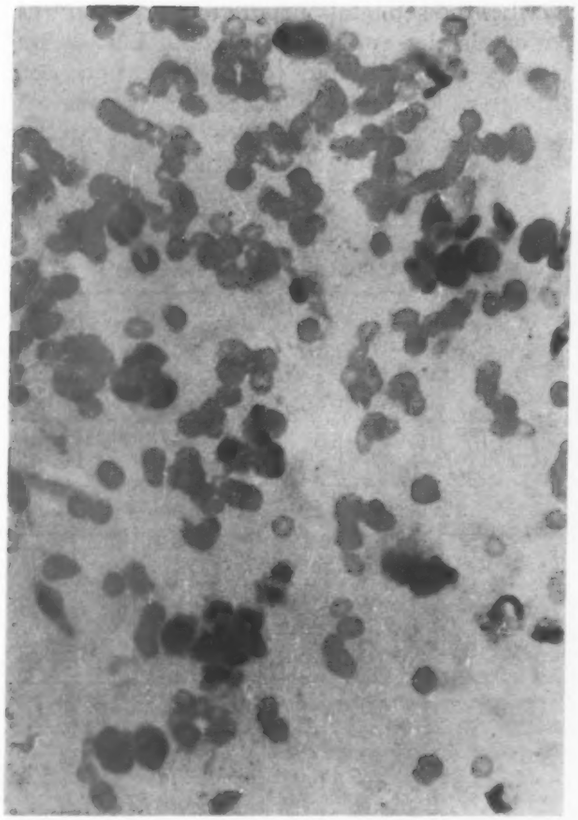

FIG. 1. Marked L.E. cell formation by the mother's blood at the time of delivery.

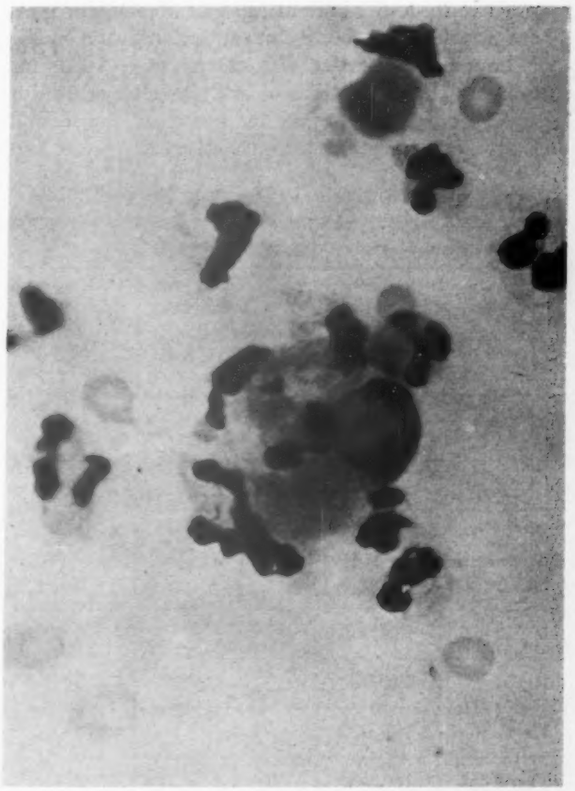

FIG. 2. The formation of a typical L.E. cell by the child's blood on the second day of life.

preparation on the mother's blood it was noted that the clot failed to retract. Although she had no petechiae, and bleeding during delivery was not excessive, her platelet count was 46,000/cu. mm. L.E. preparations remained strongly positive at this time. (Fig. 1.) Blood was drawn and the serum was saved for the determination of platelet antibodies (*vide infra*).

Within twenty-four hours after delivery her temperature rose to 101.5°F., and she was started on a therapeutic regimen of meticorten 30 mg. daily and combiotic® 1 cc. administered intramuscularly every twelve hours. She was given a high protein, low salt diet. Her temperature gradually returned to normal over the next forty-eight hours. A full-blown picture of the nephrotic syndrome was present as evidenced by moderate anasarca, hypoalbuminemia (1.6 gm. per cent), massive proteinuria (9 gm./day), blood cholesterol of 240 mg. per cent, and blood pressure of 130/86 mm. Hg. Following delivery her hemoglobin dropped to 8 gm. per cent and a transfusion of 1,000 cc. of whole blood was administered. The Coombs' test was repeatedly negative.

Two weeks after delivery her temperature again rose to 102°F. without any evidence of a focus of infection. Three blood cultures were sterile. She remained febrile despite an increase of meticorten to 60 mg. administered daily. When treatment was changed to hydrocortisone 200 mg. administered daily, her temperature gradually returned to normal and remained so. The progress of her platelet counts, clot retraction and L.E. tests are depicted in Table I. Over the ensuing two months her general condition gradually improved. The edema gradually cleared and the serum albumin rose to normal levels. Urinary excretion of protein diminished to 0.7 gm. per twenty-four hours. Azotemia, which had been present, gradually disappeared. She was discharged December 4, 1956 with advice to continue on a low salt diet and hydrocortisone 80 mg. daily. When seen in the follow-up clinic six months later she had continued to do remarkably well despite reduction of hydrocortisone to 100 mg. daily. Lupus preparations varied from 0 to 1 plus (scale of 0 to 4 plus). The platelet counts remained in the range of 150,000 to 200,000/cu. mm.

The Child

Aside from prematurity, the child appeared normal at birth. There were no purpuric lesions or other evidences of bleeding. The physical examination revealed no abnormalities. Examination of the urine was within normal limits. The hemoglobin was 14.5 gm. per cent; white blood cells, 8,350 cu. mm. with a normal differential count. The platelet count at the

end of twenty-four hours of life was 30,000/cu. mm. There was no appreciable clot retraction at the end of four hours. The serum was stored at −10°C. for subsequent determinations of antiplatelet agglutinins (*vide infra*). Examination of his blood on the second day of life by several technics disclosed weak but

TABLE I
THE PROGRESS OF THE PLATELET COUNT, CLOT RETRACTION AND L.E. PREPARATION IN THE MOTHER

Date	Platelets (cu. mm.)	Clot Retraction after 24 Hr. (scale 0 to 4+)	L.E. Cells (scale 0 to 4+)
10/8/56	46,000	0	4+
10/13/56	78,000	2+	4+
10/22/56	180,000	4+	2+
10/23/56	124,000	4+	2+
10/28/56	132,000	4+	2+
10/31/56	146,000	...	...
11/9/56	188,000	4+	1+
11/14/56	161,000	4+	1+
12/4/56	160,000	4+	1+
12/18/56	138,000	4+	1+
1/22/57	158,000	4+	1+

definite L.E. cell formation. (Fig. 2.) Typical L.E. cells were rarely seen; rosettes and droplet cells were more frequently observed in the clotted blood preparations. The progress of the child's platelet counts, clot retraction and L.E. tests are recorded in Table II. No hormone therapy was given, and aside from an upper respiratory infection at the age of nine days, his development was uneventful. He was artificially fed. At the time of discharge at the age of two months, he weighed 6 pounds and 7 ounces (2.4 kg.). The platelet count had spontaneously risen to normal levels. Follow-up studies at the end of six months of life revealed a perfectly normal male child.

COMMENTS

Harrington [*12*] has claimed that congenital purpura may occur in two situations. In the first or "primary" type, the mother never has had thrombocytopenia. Purpura in these children he ascribes to fetal-maternal incompatibility, with isoimmunization. In the "secondary" form in which the mother has had purpura, he ascribes the neonatal purpura to placental transfer of platelet antibodies. Epstein, Lozner and Cobbey [*13*] and Tullis [*8*] report that neonatal thrombocytopenic purpura of some degree will occur in over half the babies born to mothers with previous thrombocytopenic purpura. In a

TABLE II
THE PROGRESS OF THE PLATELET COUNT, CLOT RETRACTION AND L.E. PREPARATION IN THE CHILD

Date	Platelets (cu. mm.)	Clot Retraction after 24 Hr. (scale 0 to 4+)	L.E. Cells (scale 0 to 4+)
10/8/56	30,000	0	1+
10/13/56	48,000	0	0
10/17/56	92,000	2+	0
10/23/56	93,000	...	0
10/26/56	156,000	4+	0
10/31/56	176,000	4+	...
11/9/56	170,000	...	0
11/16/56	226,000	...	...
11/26/56	270,000	4+	0
11/29/56	214,000	...	...
12/18/56	170,000	...	...
1/22/57	212,000	...	...

study of twelve infants with congenital thrombocytopenic purpura, Tullis [*8*] was able to demonstrate the presence of platelet antibodies in eight cases. Of sixteen mothers who gave birth to purpuric infants, ten had positive platelet antibody tests. He agreed with Harrington that congenital purpura may result from the two causative mechanisms mentioned.

The results of the platelet antibody determinations conducted on the serums of the mother and child in the report are depicted in Table III. It will be seen that the serums of both mother and child demonstrated the presence of platelet antibodies. It is doubtful whether the slightly lower titer of the infant's serum drawn on October 11, 1956 is statistically significant. Unless one postulates the unlikely coexistence of S.L.E. and idiopathic thrombocytopenic purpura in the

mother, the findings in this unusual situation suggest that thrombocytopenia as it occurs in S.L.E. may in some if not all cases be due to autoimmunization. To our knowledge, this is the first case of congenital thrombocytopenia to be reported in S.L.E.

TABLE III
RESULTS OF PLATELET ANTIBODY TESTS PERFORMED ON SERUMS OF MOTHER AND CHILD*

	Percentage Change in Platelet Count	
	45 minutes	90 minutes
Control serum	+2	+2
Mother's serum, 10/10/56	−12	−20
Child's serum, 10/10/56	−8	−25
Child's serum, 10/11/56	−11	−15

* The authors are indebted to Dr. James L. Tullis who kindly performed these determinations. By this method [*8*] a standard platelet suspension is incubated with control and test serums and the percentage change in platelet count is recorded at the end of forty-five and ninety minutes. Normal serums when tested in this manner will show a maximal fall of 5 per cent at the end of ninety minutes.

It has been demonstrated that L.E. factor [*2*] and antiplatelet activity [*7*] are present in the gamma globulin fraction of blood serum. Although the evidence as yet remains inconclusive, several investigators have proposed that the humoral factors responsible for these phenomena are true antibodies. Miescher [*14*], Nathan and Snapper [*7*] and Holman [*3*] have demonstrated the quantitative removal of L.E. cell activity from serum by adsorption with leukocyte nuclei. These investigators have proposed that the antigen is contained in the cell nucleus (i.e., nucleoprotein or one of its components). Tullis [*7*] has reported reversal of positive platelet antibody tests to negative by the prior incubation of the test serums with human platelets. These adsorption studies appear to be specific, and for the time being suggest an immunologic relationship.

Passive transfer of maternal antibodies to the fetal circulation has been known for over fifty years [*15*]. In the case of certain antibodies the levels in the newborn approximate those of the mother [*16,17*]. It is interesting that there is a close parallelism between gamma globulin concentration in the newborn and a few antibodies studied. Moore et al. [*18*] have shown that in most instances the gamma globulin content at birth is about equal to that found in the mother's circulation. Evidence is rapidly accumulating that the newborn is unable to synthesize gamma globulin and receives its entire complement from the mother [*19*].

The close parallelism between the clinical state of hypogammaglobulinemia and inability to form antibodies is well known. The newborn, furthermore, is unable to synthesize antibodies during the first month of life when gamma globulin production also is at a standstill [*20*]. The disappearance curves of passively acquired gamma globulin and of antibodies in the newborn closely follow the same rates of decay [*21*]. While the exact quantitative and biological relationship of antibodies to gamma globulin remains to be elucidated, it appears nevertheless that the two are very intimately associated.

The humoral factors responsible for L.E. cell formation and thrombocytopenia were evanescent in the newborn of this report. While serial platelet antibody determinations were not made, the rapid spontaneous return of the baby's platelet count to normal suggests a low level of placental transmission. L.E. cell formation of the baby's blood was considerably less intense when compared with the mother's blood, and could be demonstrated only during the first few days of life. Osborn et al. [*16*] reported that the titer of diphtheria antitoxin in the circulation of premature babies is less than that of the maternal blood. The prematurity of the baby in this report could be responsible for a reduced inoculum of antibodies (e.g., L.E. factor, platelet agglutinins) received from the mother. It is interesting to note that in the patient of Bridge and Foley [*10*], despite the absence of prematurity, minimal L.E. cell activity was demonstrated in cord blood, although it was quite marked in the maternal blood. Unless one assumes that L.E. factor is quickly removed from the fetal circulation by tissue (cell nuclei) fixation, it appears that the placental membrane is not readily permeable to this substance. The blood of the baby described by Bridge and Foley was re-examined only seven weeks after birth and at that time the results were "indefinite." One can, therefore, assume that all L.E. factor actually may well have disappeared in the interim.

Berlyne et al. [*11*], although they failed to mention the quantitative relationship of the L.E. phenomenon in mother and child at the time of delivery, noted that the child who was breast-fed had the greatest intensity of L.E. cell formation. Parenthetically it should be mentioned that the mother of this child was a strong L.E. cell former during the period of breast feeding. Although breast milk contains maternal antibodies, to our knowledge L.E. factor has not as yet been demonstrated in this secretion. It seems possible that the stronger L.E. cell reaction in the breast-fed infant may have been due to L.E. factor transmission in the mother's milk.

The clinical significance of the demonstration of L.E. factor in the infant's blood is evidently negligible. To our knowledge no child born to a mother with S.L.E. has demonstrated any manifestations of this disease other than the evanescent L.E. cell phenomenon and congenital thrombocytopenia reported here. While S.L.E. is not an infrequently occurring disorder, examples of familial occurrence are decidedly rare. In a recent report Glagov and Gechman [*22*] accepted three examples, adding one of their own. A mother-sibling relationship existed in only two of the four cases and both children were well into their teens when the disease became manifest. In neither case was the mother known to be ill with S.L.E. at the time of pregnancy.

In a review of twenty-nine patients with S.L.E., involving forty-two pregnancies, Friedman and Rutherford [*23*] reported an increased incidence of premature births and spontaneous abortion although fertility did not appear to be affected by the underlying disease. They further came to the conclusion that pregnancy, in general, did not adversely affect the lupus condition. On the basis of their experiences they are loathe to suggest interruption of pregnancy in a patient with S.L.E. While they made no mention of a prolonged follow-up study on the viable offspring, these authors point out that none of the newborns revealed any evidence of the maternal disease. In fact, in their series there were only two deaths among twenty-nine viable births. These deaths were ascribed to prematurity and a cord complication, respectively. An autopsy performed on a twenty-four-week old fetus delivered by a mother with extensive histologic lesions of S.L.E. failed to show any lesions of this disease on gross and microscopic examination [*24*]. Fetal death was ascribed to prematurity.

It therefore appears that while L.E. factor can pass the placental barrier, this is only a passive process and does not result in any self-perpetuating neonatal or postnatal disorder.

SUMMARY

A case report is presented of a pregnant adolescent with systemic lupus erythematosus and thrombocytopenia who gave birth to a premature child with thrombocytopenia and evanescent evidence of L.E. factor activity. Serologic studies disclosed the presence of platelet agglutinus in the serums both of the mother and newborn. This study demonstrates the placental transfer of humoral factors responsible for L.E. cell formation and congenital thrombocytopenia in a patient with S.L.E. The significance and implications of this chance observation are discussed.

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Anomalous Pulmonary Venous Drainage*

Diagnostic Value of Bronchospirometry

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In a recent review of diagnostic methods in the study of left to right shunts, Grant [*1*] listed four methods that had been found to be of particular value: "electrocardiography, blood-gas analysis, contrast radiography, and dye-dilution methods." The purpose of this paper is to demonstrate the value of differential bronchospirometry in the diagnosis of one type of left to right shunt, due to anomalous pulmonary venous drainage.

CASE REPORT

The patient (C. Qui.), an eighteen year old white girl, had noted mild non-progressive exertional dyspnea for many years. No other cardiorespiratory symptoms were present. The blood pressure was 94/60 mm. Hg, heart rate 78, with normal sinus rhythm. Cyanosis, clubbing and edema were absent. The lungs were clear. Cardiac examination revealed the point of maximum impulse to be in the fifth left interspace at the mid-clavicular line. M_1 was greater than M_2, and M_1 and M_2 were split. A_2 was greater than P_2, and both were widely split. The degree of splitting of P_2 did not increase on inspiration. A grade 3 moderately harsh systolic murmur was heard over the precordium, maximally at the pulmonary area, transmitted to the axilla and aortic area. Prominent pulsations were present in the pulmonary area and in the fourth left interspace just to the left of the sternum.

Fluoroscopy revealed a bilateral increase in pulmonary vascular markings. No true hilar dance was noted but the pulmonary artery was moderately enlarged with increased pulsations. The left ventricle was not enlarged; the left atrium was slightly enlarged. The right atrium and ventricle were moderately enlarged. X-ray films revealed similar findings. (Fig. 1.) The electrocardiogram was considered typical of right ventricular hypertrophy, with an "incomplete right bundle branch block pattern" noted in V3R and V1. (Fig. 2.) The clinical diagnosis was congenital heart disease, enlarged heart, interatrial septal defect and/or anomalous pulmonary venous drainage, normal sinus rhythm, class 1 B.

Cardiac catheterization was performed with a double-lumen Cournand catheter.† The pressure and blood oxygen content data are given in Tables I and II. The catheter tip was easily manipulated from the right atrium into a right pulmonary vein leading to the right upper lung field (Figs. 3 and 4) and the right lower lung field (Fig. 5), establishing the diagnosis of anomalous pulmonary venous connection and drainage. The catheter tip could not be manipulated through an intratrial septal defect, although the presence of this additional lesion could not be ruled out. Pulmonary venous wedge pressures were obtained from the right upper and lower lung fields. (Figs. 6 and 7.) Pulmonary artery and pulmonary artery wedge pressures were also recorded. (Fig. 8.)

The problem subsequently arose as to whether or not the entire right pulmonary venous drainage was into the right atrium. Bronchospirometry was therefore performed one week after cardiac catheterization. A Carlens catheter was passed into the trachea in the usual manner so as to separate the ventilatory pathways of the right and left lungs. A Cournand arterial needle was then inserted into the right brachial artery. Different gas mixtures were then applied to the two lungs (Table III), and repeat measurements of arterial blood saturation made. The data were interpreted as suggesting strongly that right pulmonary venous drainage was mainly into the right atrium.

The patient was then followed in the cardiac clinic. In June 1957 cardiac catheterization was repeated. There had been no change in symptomatology and exercise tolerance in the fifteen-month interval. The only new finding on physical examination was the appearance of a faint high-pitched diastolic blow at the pulmonary area. Electrocardiographic and radiographic findings were unchanged.

Cardiac catheterization was performed with a triple-lumen catheter on this occasion. The middle

† The zero pressure level was 5 cm. below the sternal angle of Louis.

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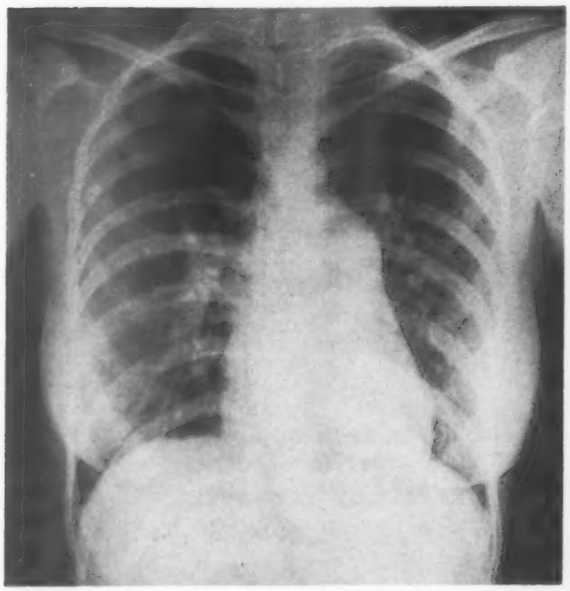

FIG. 1. Posteroanterior film of the chest showing enlargement of the pulmonary artery and its major branches, and increased pulmonary vascular markings. The transverse diameter of the heart is increased.

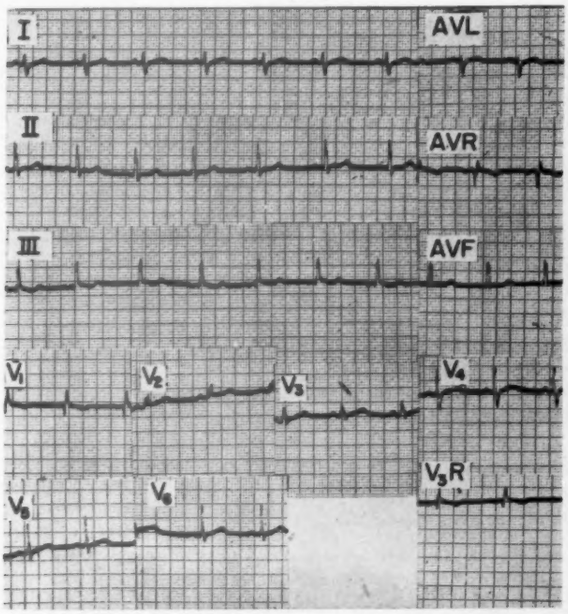

FIG. 2. Electrocardiogram demonstrating right ventricular hypertrophy.

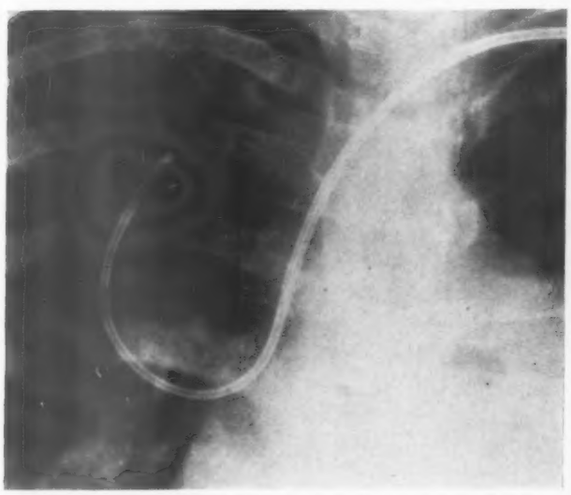

FIG. 3. Spot film during the first cardiac catheterization. The tip of the double-lumen catheter is wedged in a right upper lobe pulmonary vein, passing into the lung field directly from the right atrium.

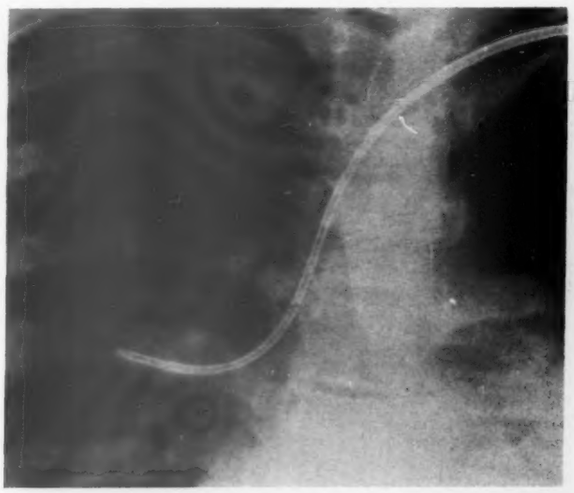

FIG. 4. The same as Figure 3, but the tip has been partially withdrawn and is lying free in the pulmonary vein.

opening is 12 cm. from the tip, and the proximal opening 27 cm. from the tip. On this study, the catheter tip was passed through an interatrial septal defect into the left atrium and left ventricle. The right sided anomalous pulmonary veins were again easily entered. Intracardiac pressures were obtained from various sites. Surgical correction of both congenital lesions was suggested but refused by the patient.

COMMENTS

The major purpose of this study is to illustrate the utility of bronchospirometry in the diagnosis of left to right shunts involving differential shunting from the two lungs. Such differential shunting occurs in anomalous pulmonary venous drainage, as in anomalous pulmonary venous connection or in interatrial septal defect [*2*]. Under these conditions, administration of gas

TABLE I
PRESSURE DATA OBTAINED DURING CARDIAC CATHETERIZATION

Date (mm. Hg)	Cardiac Catheterization (3/26/56)	Cardiac Catheterization (6/17/57)
Pulmonary artery (s/d,m)*	18/9, 13	18/7, 12
Pulmonary artery wedge (m)	5	3
Right ventricle (s/d)	20/2	22/4
Right atrium (m)	3	4
Superior vena cava (m)	.....	4
Pulmonary vein (m)	3	4
Pulmonary vein wedge (s/d,m)	21/8, 13† 11/4, 6‡	20/7, 12‡
Left ventricle (s/d)	.....	108/6
Femoral artery (s/d,m)	123/61, 88	.....
Brachial artery (s/d,m)	121/71, 82	.....

* s = systolic, d = diastolic, m = mean.
† Right lower lung field.
‡ Right upper lung field.

TABLE II
CARDIAC AND ARTERIAL BLOOD O_2 CONTENTS DURING CARDIAC CATHETERIZATION

Site	O_2 Content (vol. %)	O_2 Capacity (vol. %)	O_2 Saturation (%)
Cardiac Catheterization (3/26/56)			
Inferior vena cava	14.9	....	..
Superior vena cava	12.3	....	..
High right atrium	16.6	....	..
Mid-right atrium	16.3	....	..
Low right atrium	16.5	....	..
Tricuspid right atrium	16.5	....	..
Tricuspid right ventricle	16.7	....	..
Apex right ventricle	16.6	....	..
Outflow tract right ventricle	17.1	....	..
Main pulmonary artery	17.4	....	..
Right pulmonary artery	17.0	....	..
Right brachial artery	18.2	19.3	96
Right femoral artery	18.2	19.3	96
Right upper lobe pulmonary vein*	18.2	....	..
Right upper lobe pulmonary vein†	18.2	....	..
Right lower lobe pulmonary vein*	18.0	....	..
Right lower lobe pulmonary vein†	18.1	....	..
Cardiac Catheterization (6/17/57)			
High superior vena cava	6.0	....	..
High right atrium	10.3	....	..
Inferior vena cava	13.5	....	..
Mid-right atrium	15.0	....	..
Right lower lobe pulmonary vein†	16.6	....	..
Right lower lobe pulmonary vein*	17.7	18.7	97
Right upper lobe pulmonary vein†	17.7	18.7	97
Right upper lobe pulmonary vein*	18.1	19.1	97
Left ventricle	17.6	....	..

* Wedged sample.
† Unwedged sample.

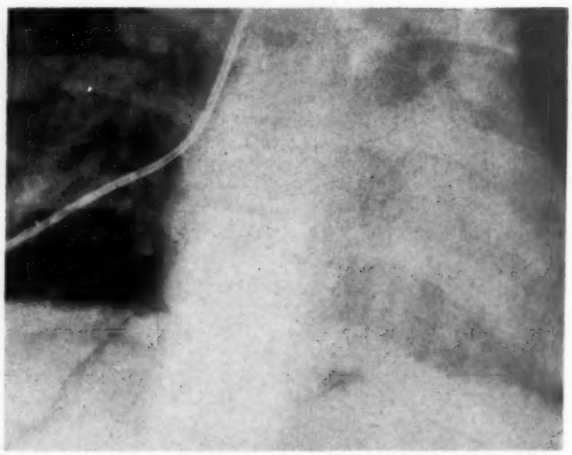

FIG. 5. The tip of the catheter has passed from the right atrium into a right lower lung field pulmonary vein.

mixtures containing differing oxygen contents to the two lungs will have varying effects upon peripheral arterial oxygen saturation depending on whether the high or low oxygen content mixture is given to the lung with anomalous drainage. In the present case, when room air was inhaled by both lungs (Table III) the arterial oxygen saturation was 94 per cent. When pure nitrogen (O_2 content 0.16 per cent) was given to the right lung (the side of the anomalous pulmonary venous connection), and 24 per cent O_2 to the left lung, the peripheral arterial oxygen saturation remained unchanged after ten minutes. When the gas mixtures were reversed, and nitrogen inhaled by the left lung, arterial saturation fell rapidly to 73 per cent within three minutes. These findings together with the anatomic demonstration of anomalous pulmonary venous connection involving the right upper and right lower lung field led to the diagnosis of total unilateral (right sided) anomalous venous connection and drainage. Ideally, continuous recording of arterial oxygen

TABLE III
ARTERIAL BLOOD SATURATION DURING BRONCHOSPIROMETRY

Gas Mixture Inhaled	Arterial Oxygen Saturation (%)
Both lungs, room air	94
Left lung, 24% O_2, 10 min	..
Right lung, pure N_2, 10 min	94
Left lung, pure N_2, 3 min	..
Right lung, 24% O_2, 3 min	73

saturation or tension, during inhalation of differential gas mixtures by the two lungs, would be the most desirable method of demonstrating differential left-right shunting from the two lungs.

There are no prior reports illustrating the utility of bronchospirometry coupled with arterial blood gas measurements in this fashion. Arvidsson [*3*] employed bronchospirometry alone to measure differential lung function in anomalous pulmonary venous drainage. Diminished oxygen uptake was found on the involved side, with the patient at rest and during exercise. Mankin and Burchell [*4*] had originally suggested "bronchospirometric studies with recording of the arterial oxygen saturation during differential breathing of nitrogen or oxygen" but published no actual data. Cooke and coworkers [*5*] reported normal oxygen uptake and vital capacity in a lung which partially drained into the inferior vena cava.*

Another point of interest in this patient is the form of the curve obtained by wedging the tip of the catheter in a pulmonary vein. During the first study, a pulmonary vein wedge pressure curve from the right upper lobe resembled a damped pulmonary artery curve. The vein wedge pressure curve from the corresponding right lower lobe (Fig. 7) was virtually identical to the pulmonary artery curve (Fig. 8) both in form and absolute pressure level. (Table I.) On the other hand, the mean pressure in the pulmonary artery wedge position (Fig. 8) was similar to that in the free vein. (Figs. 6 and 7, and Table I.) The form at the wedged pulmonary vein pressure again resembled that of the pulmonary artery during the second cardiac catheterization.

Despite the similarity in form, however, between the pulmonary artery curve and the pulmonary vein wedge curve, it should be noted that the interval between the QRS and upstroke of the pressure curve is 0.08 to 0.10 second for the pulmonary artery curve (Fig. 8), but is 0.18 to 0.21 for the pulmonary vein wedge pressure (Figs. 6 and 7). The oxygen content (Table II) in the pulmonary vein wedge position is similar to, but not lower than, that obtained from the free pulmonary vein position. Unsaturated blood was not obtained from the pulmonary vein wedge site.

* These workers [*3,5*] did not perform arterial puncture at the time of bronchospirometry and arterial oxygen saturations were not determined.

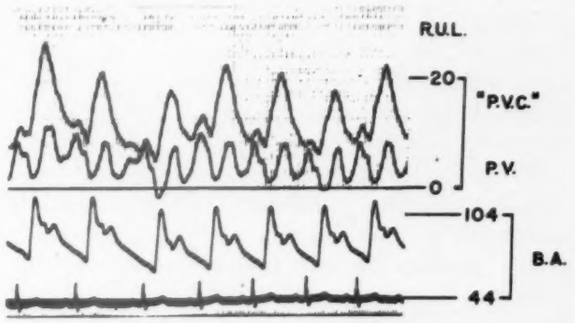

FIG. 6. Brachial artery, free pulmonary vein (P.V.) and wedged pulmonary vein pressure ("P.V.C.") in the right upper lobe. The latter curve is damped and the interval between the QRS and the onset of pressure rise is 0.18–0.20 seconds.

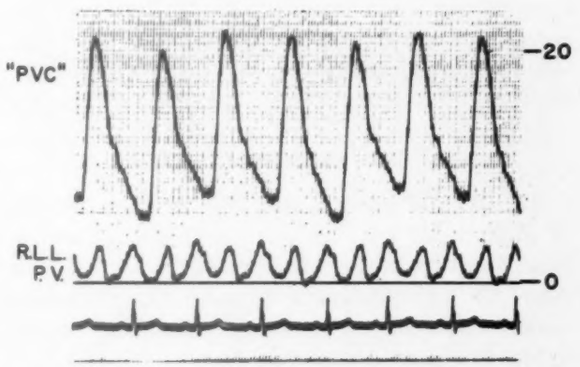

FIG. 7. Pulmonary vein curves from the right lower lung field, free (P.V.) and wedged (P.V.C.). Note that the latter curve is not damped but the QRS-upstroke interval is about 0.20 second. The wedged pulmonary vein curve form closely resembles the pulmonary artery curve form in Figure 8.

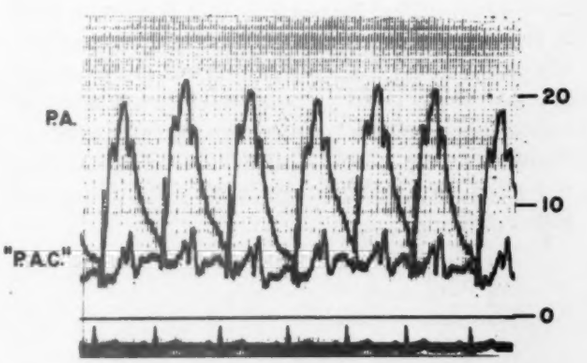

FIG. 8. Pulmonary artery and pulmonary artery wedge curves. The QRS-upstroke interval is 0.08 to 0.10 second for the former curve.

Calazel [*6*] et al. recorded pulmonary vein wedge pressures in two patients with interatrial septal defects and recorded pressure levels similar to those in the pulmonary artery. The form of the curves was not illustrated.

Hellems [*7*] was the first to show that the pressure in the wedge pulmonary vein position was higher than that in the wedged pulmonary artery position in the dog. Weissel and coworkers [*8*] also found that the form of the pulmonary vein wedge pressure resembled that of a pulmonary artery curve. Others have confirmed and contradicted these observations (Wilson et al. [*9,10*], Blount et al. [*11*], Wood [*12*], and Haddy et al. [*13*]) both as to similarity in pressure wave contour and pressure level. These divergent observations illustrate the continued problems associated with the use of wedge pressures in general. Unpublished observations on pulmonary artery wedge pressures in this laboratory [*14*] have repeatedly illustrated the difficulties in interpretation of such pressure curves.

SUMMARY

The role of bronchospirometry in evaluation of differential left to right congenital shunting from the two lungs is illustrated in an eighteen year old white girl who was found, at cardiac catheterization, to have an interatrial septal defect and anomalous pulmonary venous drainage from the right lung only. During bronchospirometry, administration of pure nitrogen to the right lung (the lung with anomalous pulmonary venous drainage) did not result in a fall in arterial oxygen saturation after ten minutes. However, administration of pure nitrogen to the left lung resulted in a rapid fall in oxygen saturation after a three-minute period. These observations suggest that blood draining the right lung in this patient does not directly reach the periphery at any time, but may only reach the systemic arterial blood after circulation through the left lung. This technic may also be of value in demonstrating differential left to right shunting from the two lungs in patients with interatrial septal defect.

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PREMENSTRUAL TENSION

DYSMENORRHEA

ENOVID

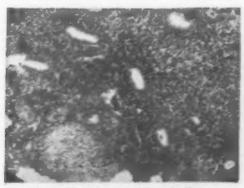
MENORRHAGIA

FOR CONTROL IN AMENORRHEA

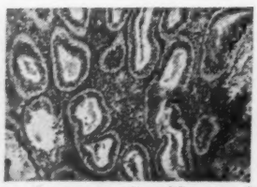
METRORRHAGIA

INADEQUATE LUTEAL PHASE

OLIGOMENORRHEA



B. M., age 30, ovarian failure. Primed with ethynylestradiol, 0.05 mg. twice a day for twenty-one days. Control biopsy after estrogen therapy showed proliferative phase.



Response after 10 mg. of Enovid daily for fourteen days revealed beginning secretory effects (fifteenth to sixteenth day) with adequate stromal stimulation.

ENOVID®

(BRAND OF NORETHYNODREL WITH ETHYNYLESTRADIOL 3-METHYL ETHER)

ORAL SYNTHETIC ENDOMETROPIN

The successful use of Enovid in amenorrhea has been reported[1-4] by various investigators.

The endometropic action of Enovid establishes a secretory (progestational or luteal) endometrium in the patient with sufficient endogenous estrogen. In others, preliminary estrogen "priming" will be required.

If a daily dosage of one tablet of Enovid is administered for twenty days and then discontinued, a menstrual period will usually occur about three days later. Therapy is resumed at the same dosage on day 5 of the newly established cycle and continued until day 25, and this schedule is repeated for the next two or three cycles. Following this, regular periods and ovulation are likely to occur in some women.

If endogenous estrogen is inadequate, a daily "priming" dose of estrogen is given for two weeks; this is followed by the administration of one tablet of Enovid for ten days. This dosage schedule is then repeated for two or three successive cycles.

Each tablet of 10 mg. contains 9.85 mg. of norethynodrel, a new synthetic steroid, and 0.15 mg. of ethynylestradiol 3-methyl ether.

1. Southam, A. L.: A Symposium on 19-Nor Progestational Steroids: Effect of Enovid in Amenorrhea and Menometrorrhagia, Chicago, Searle Research Laboratories, 1957, pp. 46-50.

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G. D. Searle & Co., Chicago 80, Illinois. Research in the Service of Medicine.

SEARLE

Avoids *Mental Cloudiness* in hypertension therapy

Rautensin (the alseroxylon fraction of Rauwolfia) offers simple, safe, effective and easy-to-manage therapy for the complex problem of hypertension. Rautensin produces a gradual and sustained drop in blood pressure ...calms and soothes the anxious patient without loss of alertness...slows accelerated pulse. Patients on this regimen show marked reduction of anxiety with a simultaneous increase in intellectual and psychomotor efficiency.[1]

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1. Wright, W. T. Jr.; Pokorny, C., and Foster, T. L.: J. Kansas M. Soc. 57:410, 1956.
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3. Moyer, J. H.; Dennis, E.; and Ford, R.: Arch. Int. Med. 96:530, 1955.

Rautensin®

The purified alkaloid complex of Rauwolfia with total therapeutic activity—minimal side effects.
Each tablet contains 2 mg. purified Rauwolfia serpentina alkaloids (alseroxylon fraction)

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Adult dosage for ACHROCIDIN Tablets and new caffeine-free ACHROCIDIN Syrup is two tablets or teaspoonfuls of syrup three or four times daily. Dosage for children according to weight and age.

TABLETS *(sugar coated)*
Each Tablet contains:

ACHROMYCIN® Tetracycline	125 mg.
Phenacetin	120 mg.
Caffeine	30 mg.
Salicylamide	150 mg.
Chlorothen Citrate	25 mg.

Bottles of 24 and 100.

SYRUP *(lemon-lime flavored)*
Each teaspoonful (5 cc.) contains:

ACHROMYCIN® Tetracycline equivalent to tetracycline HCl	125 mg.
Phenacetin	120 mg.
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Pyrilamine Maleate	15 mg.
Methylparaben	4 mg.
Propylparaben	1 mg.

Bottle of 4 oz.

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Portland physicians find that Serpasil® does more than reduce high blood pressure

Physicians in Portland, Maine, have found that Serpasil has advantages beyond its antihypertensive action:

1. With its rather pronounced central effect Serpasil calms patients who are frankly anxious or tense, as well as hypertensive.

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These facts were brought out by 450 U.S. physicians who were interviewed in a worldwide survey* conducted by CIBA. They reported that 74 per cent of 871 patients treated with Serpasil for hypertension *with anxiety-tension* had excellent or good overall response, while 80 per cent of 261 patients treated for tachycardia had good or excellent response.

Their experience offers good reason to prescribe Serpasil whenever marked anxiety-tension or tachycardia accompany high blood pressure.

SERPASIL® (reserpine CIBA) **C I B A** SUMMIT, N. J.

*Complete information about the results of this survey will be sent on request. 2/2607MB

HELPS PALSIED PATIENTS "LIVE AGAIN"

COGENTIN®

METHANESULFONATE (BENZTROPINE METHANESULFONATE)

rated the best single drug for the palsied patient[1]

- Well tolerated and markedly effective, COGENTIN *"should be added to the treatment program of every patient with paralysis agitans."*[2]
- COGENTIN *gives symptomatic relief* in all types of parkinsonism—whether postencephalitic, idiopathic, or arteriosclerotic.
- COGENTIN *provides highly selective action* such as no other current drug affords.[2] It is often of benefit in rigidity, muscle spasm, even in severe tremor.[3] The contracture of parkinsonism is relieved and posture is improved.[3]
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As COGENTIN is long-acting, one dose daily may be sufficient.

Supplied: as 2 mg. quarter-scored tablets in bottles of 100 and 1000.

1. M. Clin. North America 38:485 (March) 1954. 2. J.A.M.A. 162:1031, 1956. 3. J.A.M.A. 156:680, 1954. 4. Yale J. Biol. & Med. 28:308, 1955/56.

COGENTIN is a trade-mark of Merck & Co., Inc.

MSD

MERCK SHARP & DOHME
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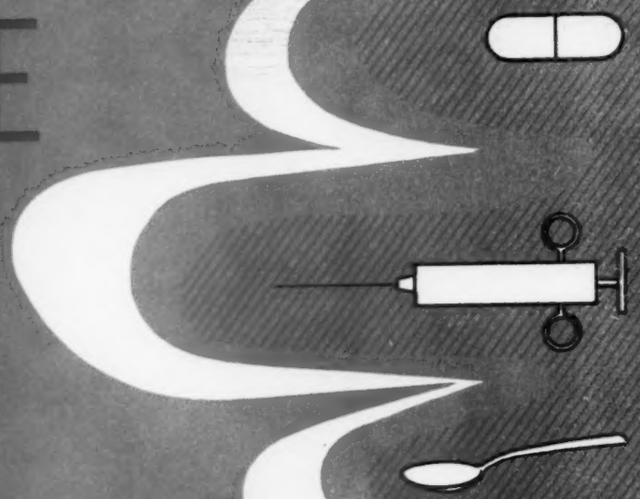
In tetracycline therapy—

FOR MAXIMUM ASSURANCE OF MAXIMUM BENEFITS



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Tetrex®

U.S. PAT. NO. 2,791,609

Tetracycline Phosphate Complex

100 mg., 250 mg. CAPSULES

Accents the antibiotic, not an additive

Bristol

why all the fuss over potassium?

Many physicians will recall when safe but potent organomercurials were first introduced. At the time there was considerable worry about possible potassium loss. Patients were instructed to take foods rich in this mineral, and not infrequently potassium supplements also were advised. After enough experience was gained, it became evident that only the exceptional case could lose enough potassium to be concerned about. And with oral organomercurial diuretics this was practically never a problem.

Why revive the subject now? Because clinical experience with nonmercurial diuretics indicates most of them have such a specific effect on potassium that with their use very real problems must be faced. Enough potassium loss can lead to digitalis toxicity or to a classical overt hypopotassemia. Since a fair percentage of cardiacs who receive diuretics are also digitalized, this excess potassium excretion is clinically serious. Clinical experience is still too limited with some nonmercurial diuretics to say just how often such loss will occur—but warnings already have been sounded by some clinical investigators as to the need for potassium supplementation.

Experience in many patients, for many years, demonstrates that potassium loss is never a problem when NEOHYDRIN® is the oral diuretic. And there is no refractoriness to this effective oral organomercurial.

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THE "WEIGH" OF ALL FLESH

for the patient who is all flesh and no will-power...

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helps the patient in spite of himself

Syndrox has a way of putting "backbone" into the obese patient.

First it curbs the desire for food, so that a moderate meal satisfies.

Then the euphoriant nature of Syndrox gives a lighter, brighter look to life—toning down the psychic urge to over-indulge.

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Mrs. H. T., a 30-year-old housewife, bore her first child at 26 years of age. After the delivery—and now for full four years—she has been unable to shed the excess pounds gained during pregnancy. Complete amenorrhea persisted for a year after birth, followed by only gradual return to more normal menses. Despite a seemingly healthy appearance, Mrs. H. T. suffers from exhaustion. Her memory is poor; she is not alert. Since the baby's birth, she has not regained her complete strength. "I feel cold all the time," she complains. "My skin and hair are dry."

PBI is 2.0 mcg.%; BMR -33; cholesterol 385 mg.%; EKG of reduced amplitude.

Based on history and findings, a diagnosis of hypothyroidism is made and thyroid substitution (3 gr. Proloid daily) prescribed. Within 4 months, her PBI rose to 5.4 mcg.%; cholesterol fell to 242; and EKG returned to normal. In view of the favorable results, therapy is continued indefinitely.

pattern of SUBCLINICAL HYPOTHYROIDISM

Highly purified natural thyroid extract, PROLOID provides all the fractions of thyroid secretion to normalize every facet of thyroid function.

Double assay—chemical and biological—assures a predictable clinical response for safe, effective long-term therapy.

PROLOID is available in 5 tablet sizes: ¼, ½, 1, 1½ and 5 grain tablets—and Proloid Powder for compounding.

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the total thyroid complex

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TARGET ACTION

specifically on the large bowel

FOR EASIER ELIMINATION

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(1,8-dihydroxyanthraquinone)

selective peristaltic stimulant

■ **smooth, overnight action** ■ **no griping** ■ **well tolerated, non-habituating**

Available in 75 mg. scored tablets and suspension.

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Double strength capsules for maximum economy and convenience.

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For lower dosage and in children.

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***In proportions proved optimal by clinical trial.**

(Marks, M. M.: Clin. Med. 4:151, 1957)

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Manufacturers of NEUTRAPEN® for penicillin reactions.

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"...in our experience procyclidine (Kemadrin) proved a worthy addition to the therapy of parkinsonism, because it afforded relief to many patients who had failed to respond to other drugs. It exerts an action against all symptoms of parkinsonism... hence it may be employed as the basic drug in commencing treatment with new cases."

Zier, A. and Doshay, L. J.: Procyclidine Hydrochloride (Kemadrin) Treatment of Parkinsonism in 108 Patients, Neurology (July) 1957.

"...in our series of 30 severe Parkinsonism sufferers, 21 obtained moderate to good relief with the use of this new agent, Kemadrin, in combination with other drugs."

Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. 123:79 (Jan.) 1956.

Smoother activity,
and *brighter expression*
with **'KEMADRIN'®**

Also indicated for the treatment of drug-induced symptoms resembling parkinsonism, developing during treatment of mental patients.

'KEMADRIN' brand Procyclidine Hydrochloride
Tablets of 5 mg., scored. Bottles of 100 and 1,000.

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"DEPRESSION ACCOMPANIED BY ANXIETY...WAS NOT SEEN..."[1] WITH THIS NEW ALKALOID OF RAUWOLFIA. OTHER UNDESIRABLE RAUWOLFIA-RESERPINE REACTIONS ARE SELDOM ENCOUNTERED OR ARE MINOR IN DEGREE.[1-3] PRODUCES SIGNIFICANTLY MORE STABLE AND SUSTAINED CONTROL OF THE TENSION-HYPERTENSION COMPLEX.[4] HIGHER DOSAGES MAY BE EMPLOYED WHERE INDICATED, WITH CONTINUED EXCELLENT TOLERATION.[1-4] ALSO PREFERRED FOR THERAPY OF ACUTE ANXIETY STATES AND CHRONIC MENTAL DISORDERS.[4,5]

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Dosage: The recommended initial dosage is 0.5 mg. twice daily for two weeks, with reduction thereafter to a minimum maintenance dosage of 0.25 mg. once daily. For greater hypotensive effect after initial period, increase dosage cautiously by 0.25 mg. daily up to a maximum daily dosage of 2.0 mg. Prescribe after meals.

1 Moyer, J. H., et al.: A.M.A. Arch. Int. Med. 96:530, 1955. 2. Moyer, J. H., et al.: South. M. J. 50:499, 1957. 3. Smirk, F. H., and McQueen, E. G.: Lancet 2:115, 1955. 4. Winton, S. S.: Internat. Rec. Med. 170:665, 1957. 5 Malamud, W., et al.: Am. J Psychiat. 114:193, 1957.

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LINODOXINE®

Linoleic Acid (Essential Unsaturated Fatty Acid) and Pyridoxine HCl

REDUCES ELEVATED SERUM CHOLESTEROL LEVELS IN A SUBSTANTIAL MAJORITY OF PATIENTS[1-5]

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bottles of 1 pint
Dosage:
1 tablespoonful t.i.d.

CAPSULES
bottles of 100 and 250
Dosage:
2 to 4 capsules t.i.d.
before meals

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5. Van Itallie, T. B.: J. Am. Dietet. A. 34:248, 1958.

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"This substance [Vitamin K_1] has added greatly to the safety of anticoagulant therapy"[1]

reverse anticoagulant-induced hypoprothrombinemia

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the only available preparation chemically identical with naturally-occurring vitamin K_1... "has a more prompt, more potent and more prolonged effect than the vitamin K analogues"[2]

Dosage: Orally, to modify anticoagulant effects: 5 to 10 mg. initially; 15 to 25 mg. for more vigorous action. Intravenously, for anticoagulant-induced bleeding emergencies, 10 to 50 mg.; may be repeated as indicated by prothrombin time response. (Some clinicians advise their patients to keep a supply of tablets on hand at all times; if gross bleeding occurs, the patients are instructed to take 10 mg. and phone the doctor.[1])

Supplied: Tablets, 5 mg., bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg., boxes of 6 ampuls.

Other indications: To normalize prothrombin time—before surgery, in obstructive jaundice, hepatic disease, impaired gastrointestinal absorption, deficiency of vitamin K in the newborn, and following the administration of antibiotics, sulfonamides, and salicylates. 'Mephyton' is a valuable addition to the physician's bag for emergency use.

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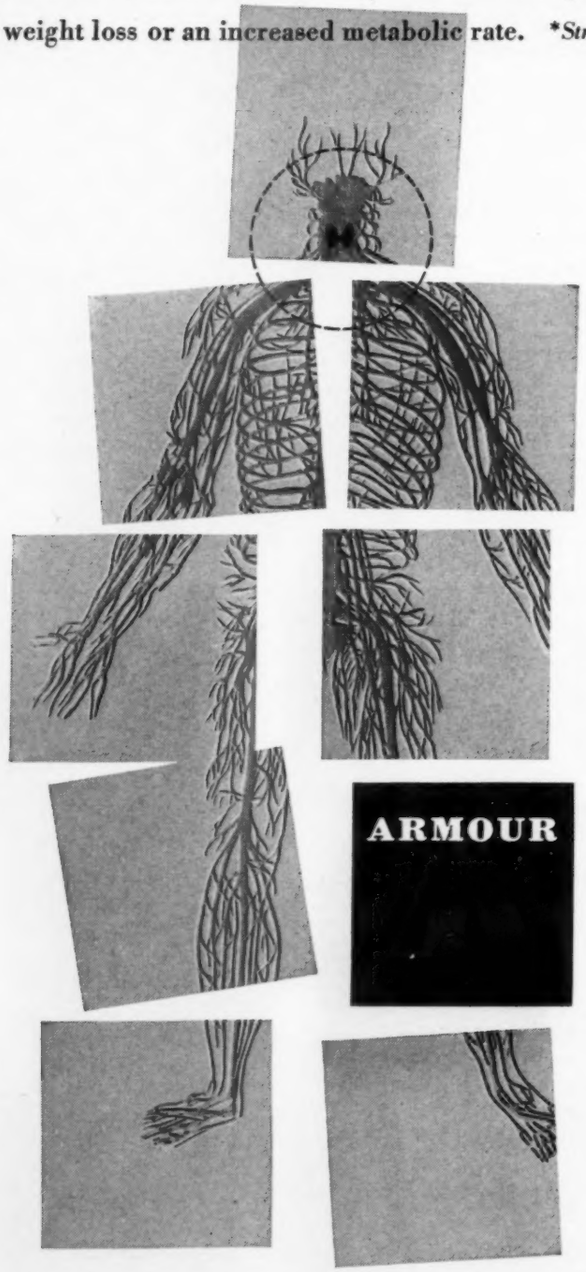
2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

Serum lipids and thyroid medication Recognition of the significant relation between serum lipids and atherosclerosis has resulted in a new interest in the role of hormones in this picture. Desiccated thyroid may reduce serum lipid levels remarkably in many patients without appreciable weight change, as reported by Strisower and co-workers.* Daily dosage ranged approximately from 3 to 5 grains. The authors conclude that treatment with desiccated thyroid need not produce adverse effects such as undesired weight loss or an increased metabolic rate. **Strisower, B., et al.: Lancet 1:120, 1957.*



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Zactirin is non-narcotic.

Zactirin is effectively anti-inflammatory.

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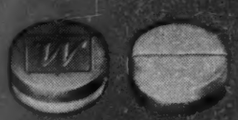

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Supplied in distinctive, 2-layer yellow-and-green tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

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gastrointestinal infections
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immediate therapeutic response

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intramuscular

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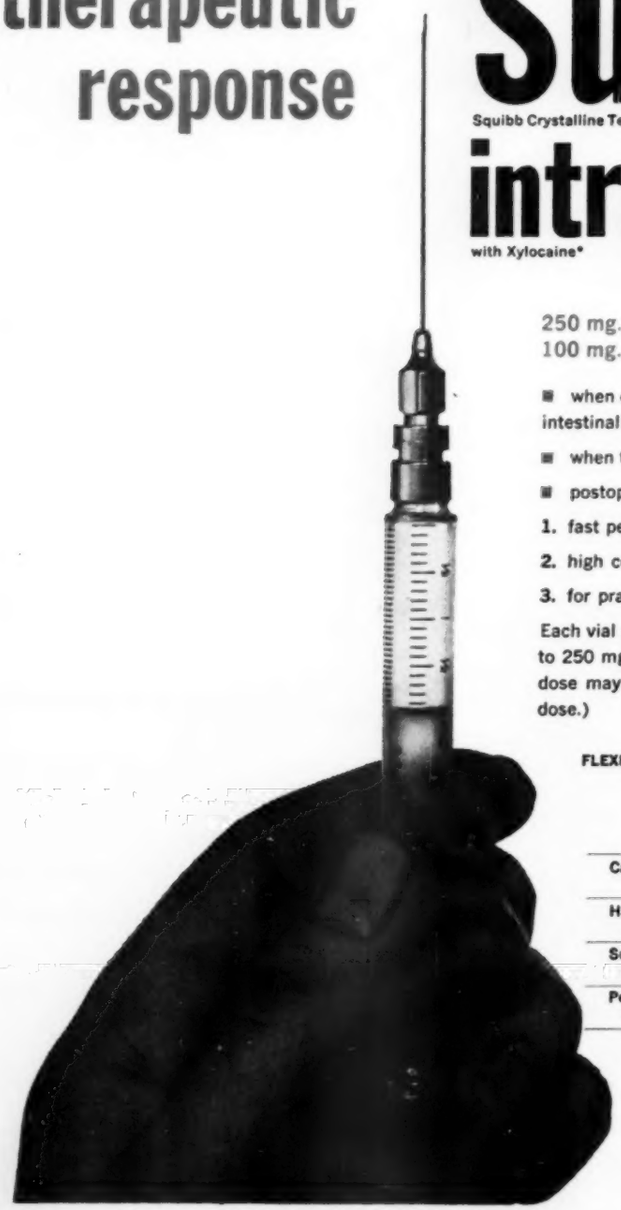

250 mg. per 1 dose vial
100 mg. per 1 dose vial

- when oral therapy is contraindicated (vomiting, dysphagia, intestinal obstruction, gastrointestinal disorders)
- when the patient is comatose or in shock
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1. fast peak blood and tissue concentrations
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3. for practical purposes, Sumycin is sodium-free

Each vial contains tetracycline phosphate complex equivalent to 250 mg., or 100 mg., of tetracycline HCl. (Note: 250 mg. dose may produce more local discomfort than the 100 mg. dose.)

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Capsules (per capsule)	250	Bottles of 16 and 100
Half Strength Capsules (per capsule)	125	Bottles of 16 and 100
Suspension (per 5 cc. teaspoonful)	125	60 cc. bottles
Pediatric Drops (per cc.—20 drops)	100	10 cc. bottles with dropper

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Squibb Quality—the Priceless Ingredient

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PALADAC
liquid vitamin supplement
Because children love the delicious orange flavor of PALADAC, there's very little chance they will forget vitamin time, even if Mother does. Since PALADAC contains a balanced formula of nine important vitamins, what more reliable and pleasant way to help assure proper vitamin intake for growing youngsters? PALADAC is even-flowing, readily miscible with milk, fruit juice, or other foods if desired, and requires no refrigeration.
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bicarbonate-regulating diuretic — **Acetazolamide Lederle**

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Primarily by regulation of bicarbonate transport	DIAMOX acetazolamide
Primarily by regulation of chloride transport	mercurials chlorothiazide

1

Advantages of DIAMOX in single-drug diuresis

DIAMOX — operating through the well-understood mechanism of *bicarbonate* transport regulation—provides ample, prolonged diuresis in the great majority of patients.

DIAMOX is virtually nontoxic . . . has not caused renal or gastric irritation . . . has no pronounced effect on blood pressure. It is rapidly excreted, does not accumulate in the body, permits convenient dosage adjustment, allows unbroken sleep. Small, tasteless, easy-to-take tablets . . . usual dosage, only one a day.

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- PREMENSTRUAL TENSION
- EDEMA OF PREGNANCY
- OBESITY

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Advantages of DIAMOX in intensive, two-drug diuresis

When intensive diuresis must be maintained, DIAMOX, alternated with an agent for regulation of *chloride* transport, has proved a regimen of choice. Through dual *bicarbonate-chloride* regulation, it produces maximal sodium-water excretion with minimal distortion of serum electrolyte patterns, greater patient comfort, lessened risk of induced drug resistance.

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- REFRACTORY TOXEMIA OF PREGNANCY

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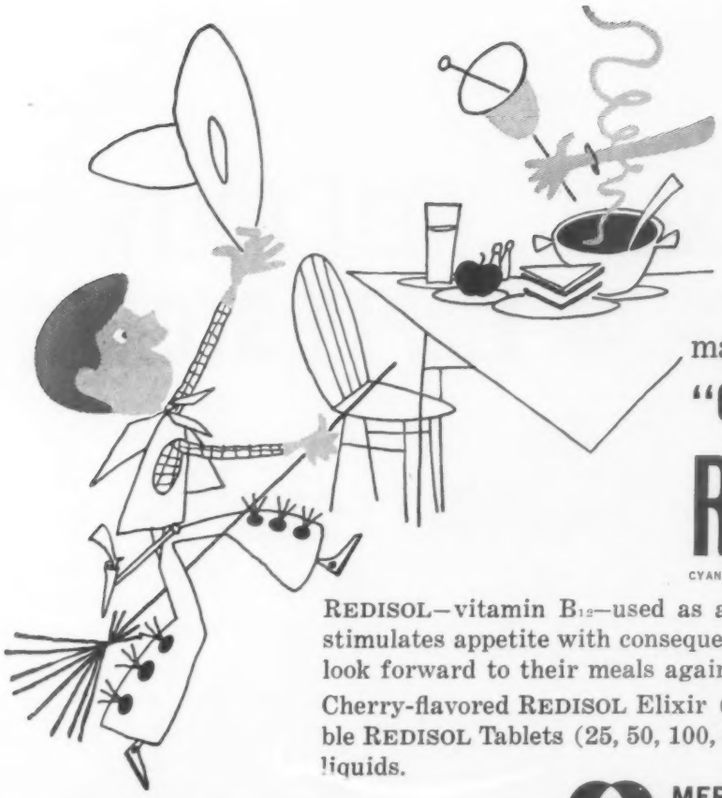

make poor eaters want to

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CYANOCOBALAMIN (CRYSTALLINE VITAMIN B_{12})

REDISOL—vitamin B_{12}—used as a dietary supplement often stimulates appetite with consequent weight gain—youngsters look forward to their meals again.

Cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) and soluble REDISOL Tablets (25, 50, 100, 250 mcg.) mix readily with liquids.

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Meprobamate and Pentaerythritol Tetranitrate

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Tablets, vials of 50, meprobamate (200 mg.) and pentaerythritol tetranitrate (10 mg.)

• serum response in 3 hours
• clinical response in days
• between-meal administration for better utilization
• WITH SIDE EFFECTS INSIGNIFICANT[1-8]

48 patients[1]—serum iron rose rapidly, Hb. response prompt	given on empty stomach in all cases—no gastric upset, diarrhea or constipation were found
91 patients[2]—significant reticulocyte response in 6 days on 2 tabs. t.i.d. in moderate hypochromic anemia—found extremely useful	even in those with peptic ulcer, gastritis, lack of side effects was reported as quite impressive —slight gastric upset in *one* patient
102 patients[3]—a remarkably sharp rise in hemoglobin levels was demonstrated	*one* complaint of mild constipation
62 patients[4]—reported to be a real advance in iron therapy	2 instances of G.I. upset disappeared with dosage adjustment
563 patients[5]—found to be efficiently absorbed and to provide predictable clinical results	only eight cases of mild intolerance— no side effects even in patients with peptic ulcer
120 patients[6]—peak reticulocyte response on fifth day	not a single complaint of upset, FERRONORD taken on empty stomach in all cases
41 patients[7]—average daily Hb. rise of 1.6%	well tolerated in peptic ulcer and gastritis patients—given on empty stomach in all cases
10,016 patients[8]—Hb. response excellent, average treatment period 4-6 weeks	only 4.39% of cases reported *any* side effects— usually adjusted with dosage

DOSAGE SCHEDULE

Average adult dose: initially, 2 tabs. b.i.d.; severe cases, 2 tabs. t.i.d.
Maintenance dose, 1-2 tabs daily. Each FERRONORD tablet supplies 40 mg. of ferrous iron.

FERRONORD Liquid, 60 cc. dropper bottles, 40 mg. iron per cc.

BIBLIOGRAPHY:

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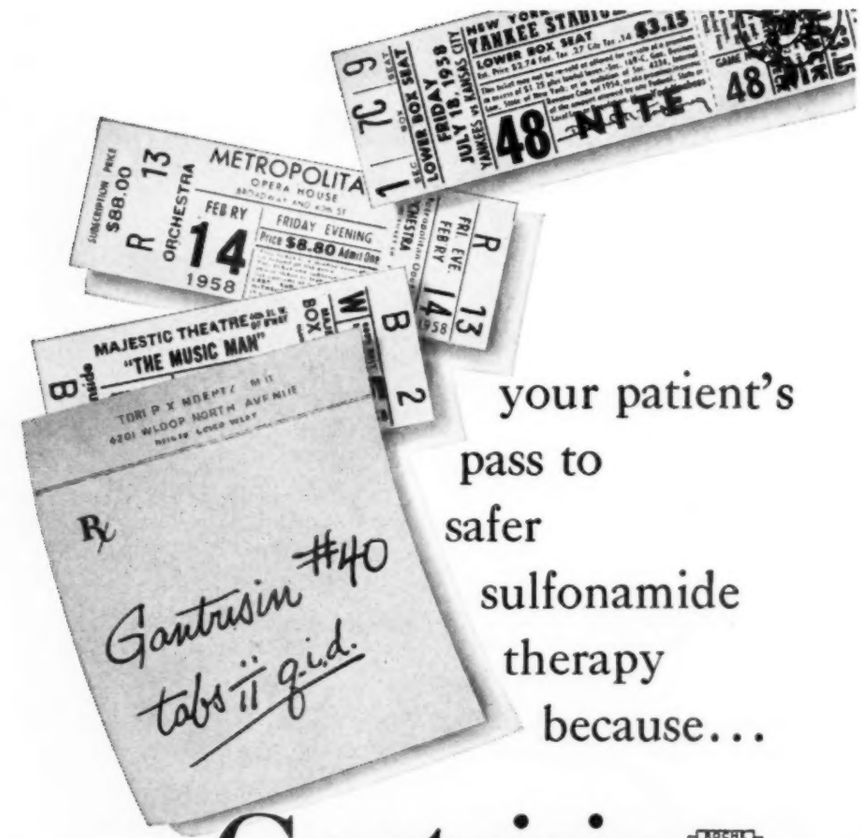

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Wilkins, R. W.: New England J. Med. 257:1026, Nov. 21, 1957.

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Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. 166:137, Jan. 11, 1958.

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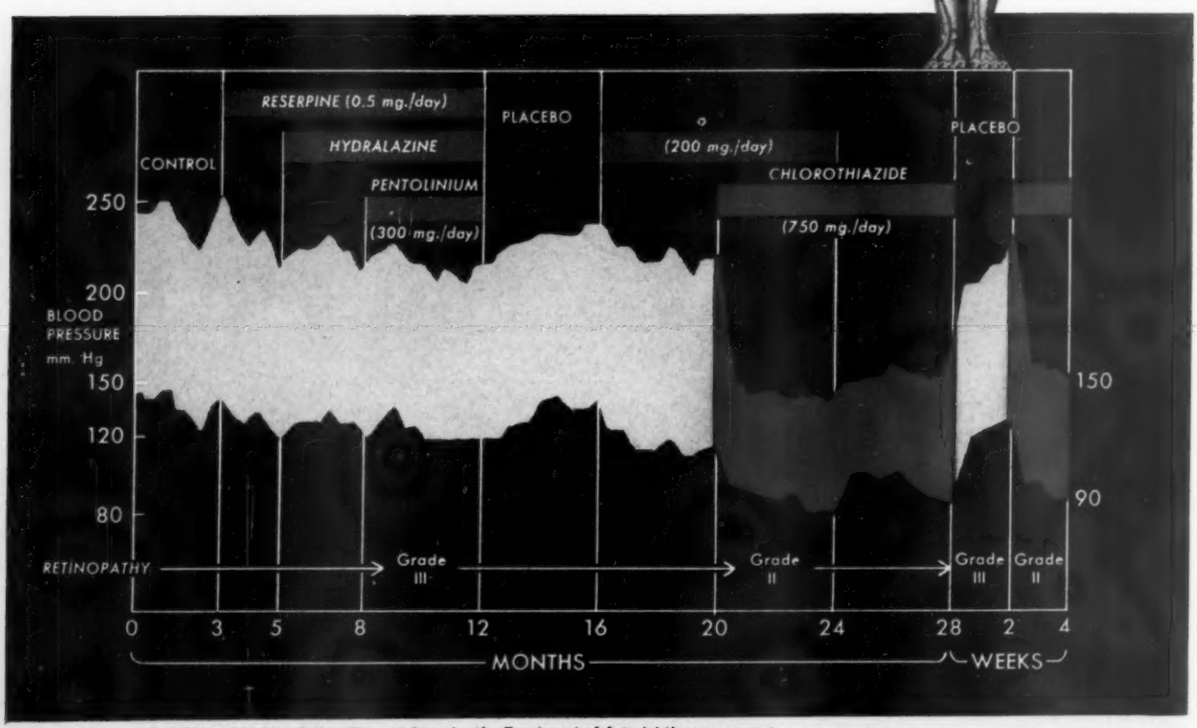

In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension," Hollander, W. and Wilkins, R. W.: Boston Med. Quart. 8:1, September, 1957.

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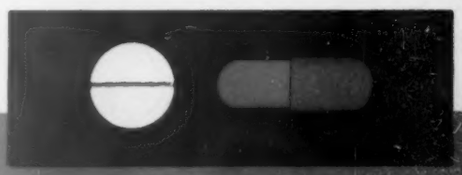
1. *Eisfelder, H.W.: Am. Pract. & Dig. Treat. 5:778 (Oct. 1954)*
2. *Freed, S.C.: G.P. 7:63 (1953)*
3. *Sherman, R.J.: Medical Times, 82:107 (Feb. 1954)*



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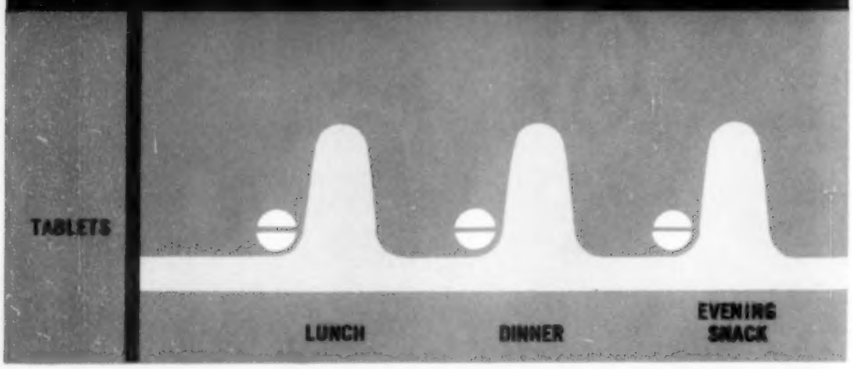

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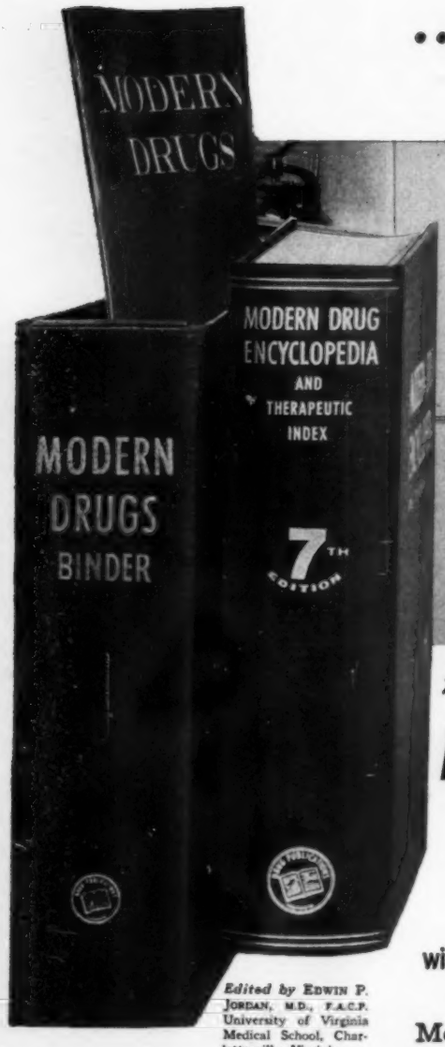

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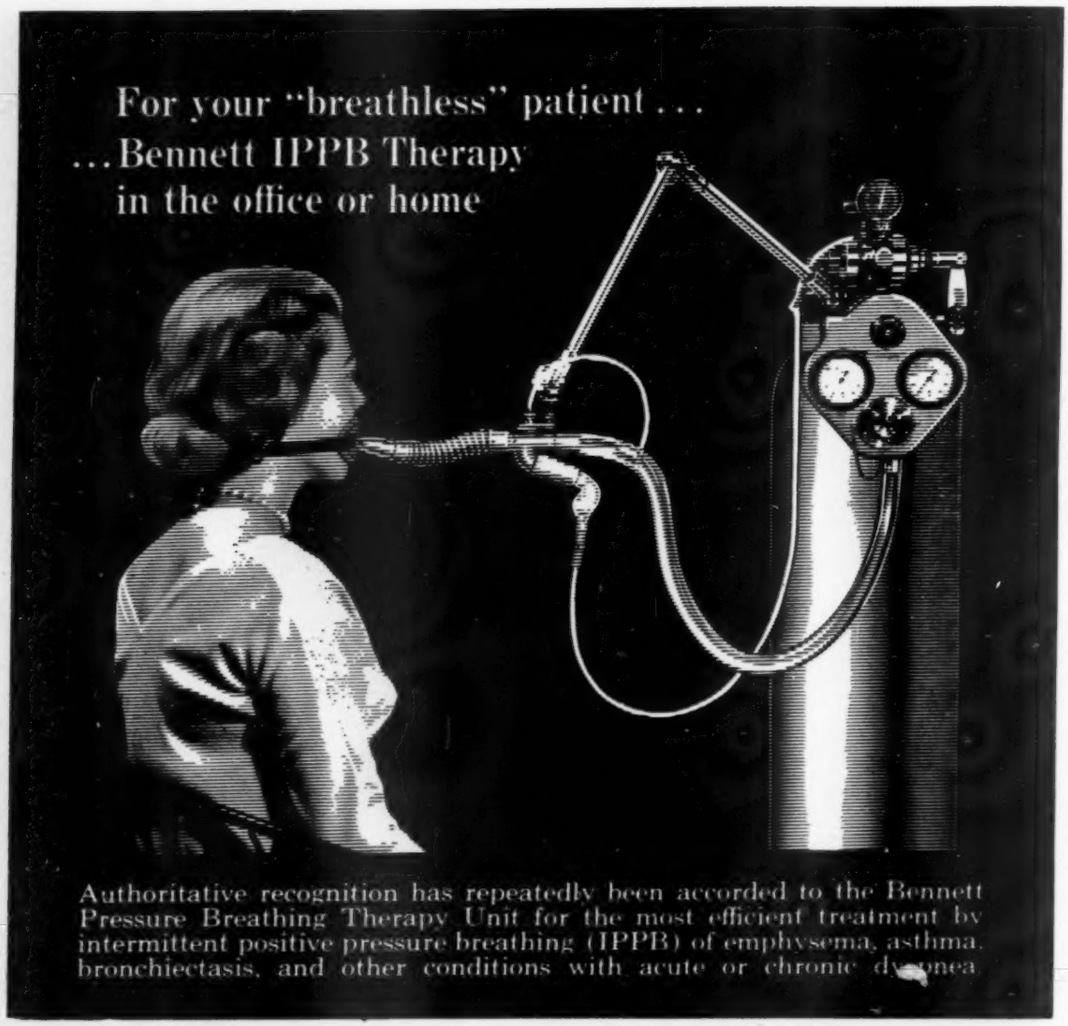

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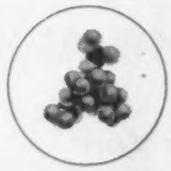

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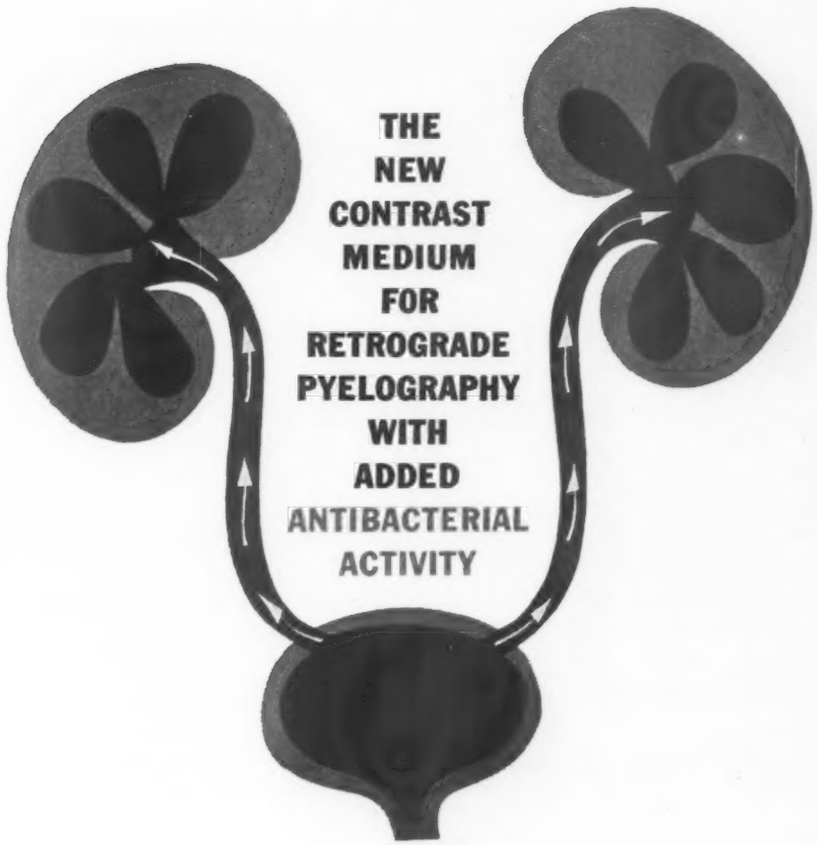

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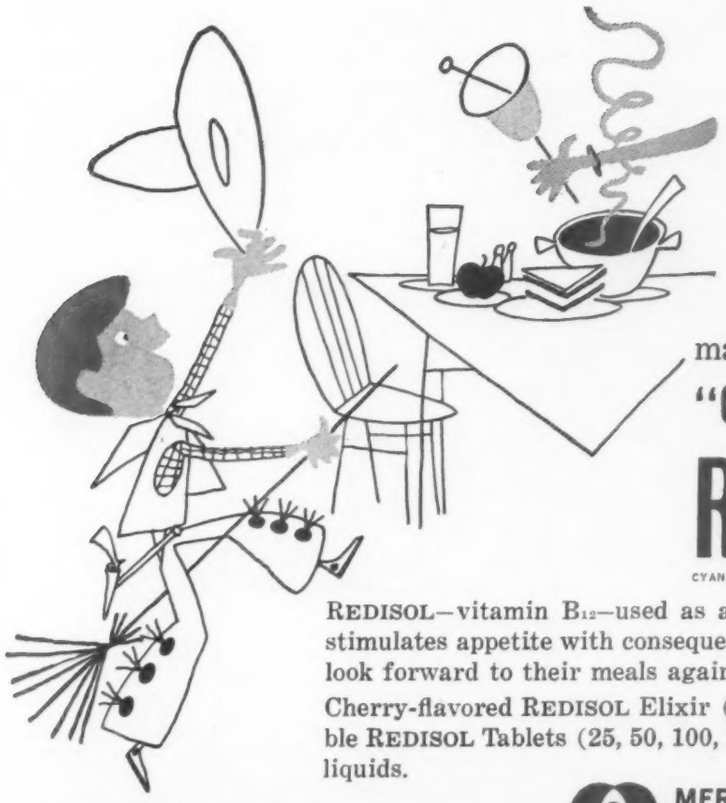

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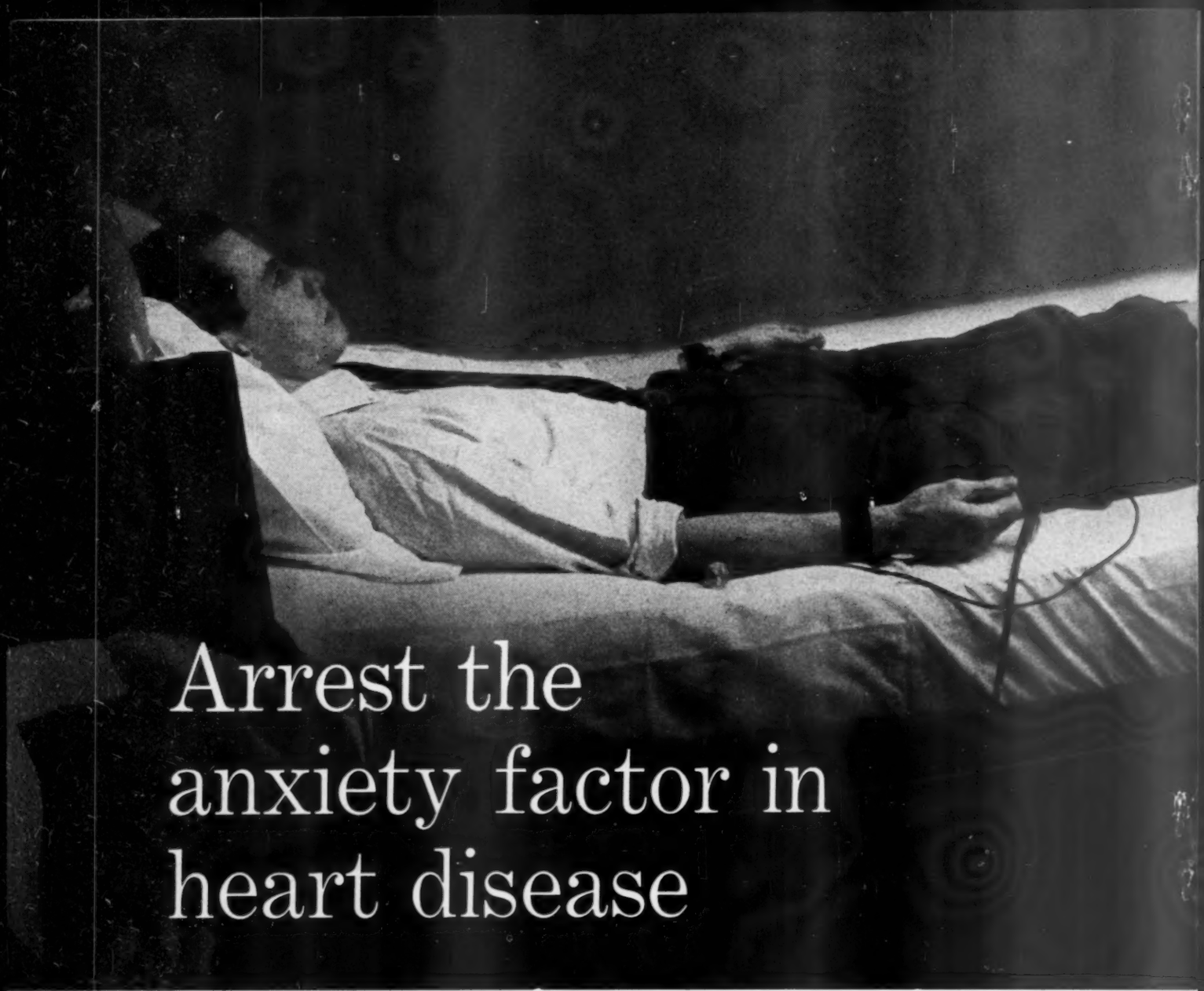

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**Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.*

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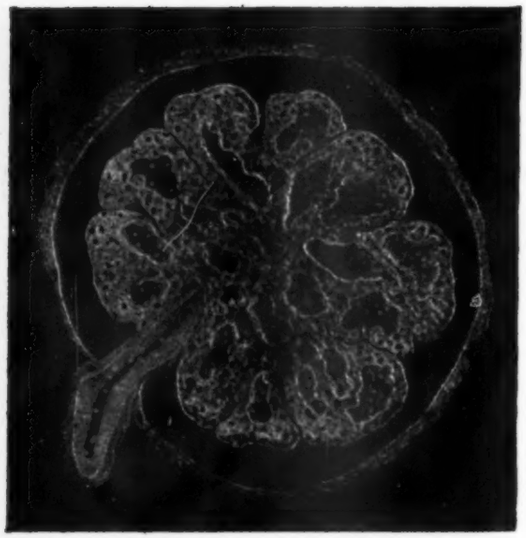
NORTHRIDGE CALIFORNIA

Advanced therapy for advancing hypertension



Apresoline®

Apresoline contributes an exclusive therapeutic action to the treatment of *moderate to severe hypertension, renal hypertension, glomerulonephritis and toxemia of pregnancy:* It not only brings blood pressure down, but is the only therapeutically acceptable agent that increases blood flow in ischemic kidneys. *Kidney damage may thus be reduced and renal function improved* when Apresoline is made part of the antihypertensive program.

Apresoline—*especially when the kidneys are involved*

Hemodynamics of hypertension	Corrective action of *Apresoline*
Renal blood flow reduced. Resulting ischemia leads to degeneration of renal tubules.	Decreases renal vascular resistance. Improves renal blood flow.
Cerebral vascular resistance increased. Oxygen consumption decreased.	Reduces cerebral vascular resistance.
Widespread vasoconstriction leading to chronic hypertension.	Decreases peripheral resistance, thus lowering elevated pressures.
Humoral factors more important than neurogenic and intrinsic factors.	Inhibits action of several vasopressor substances in blood and tissue fluids of midbrain, kidneys and periphery.

SUPPLIED: TABLETS, 10 mg. (yellow, double-scored), 25 mg. (blue, coated), 50 mg. (pink, coated) and 100 mg. (orange, coated). AMPULS, 1 ml., 20 mg. Apresoline hydrochloride per ml.

APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)

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CIBA
SUMMIT, N.J.